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IMPORTANT ANNOUNCEMENT FROM THE PUBLISHER

TO ALL CONTRIBUTORS AND SUBSCRIBERS

As from the 1st January 1961 the production of TETRAHEDRON LETTERS will be handled from the New York Office of Pergamon Press. This will involve certain slight changes in procedure, details of which are given below:

(1) Authors are requested to submit all inquiries regarding the production of TETRAHEDRON LETTERS to the Chief Sub-Editor, Pergamon Press, Inc., 122 East 55th Street, New York 22, N.Y. This address should also be used for all reprint orders for accepted communications.

(2) Carbon copies of accepted retyped communications must be returned to the Chief Sub-Editor, New York.

(3) In response to suggestions by contributors, the limit of 50 or 100 reprints has been eliminated. Authors may now order unlimited quantities of reprints, with covers if required. The reprints will be reimposed and printed separately from the Journal. A reprint order form will be sent together with notification of acceptance for publication.

(4) The pagination of TETRAHEDRON LETTERS has been altered and each issue will be numbered in continuation from the previous issue.

(5) The Author, Subject and Title Index for TETRAHEDRON LETTERS 1960, is now being prepared and will be printed with the Index for TETRAHEDRON, Vols. 8-11. The combined Index will be published in TETRAHEDRON Vol. 12, No. 4 and copies of the Index, together with a title section, will be sent to all subscribers to TETRAHEDRON LETTERS.

NOTICE TO CONTRIBUTORS

To conform with the standard procedure of American printers it has been necessary to alter the trim size of "Tetrahedron Letters" to 6" x 9". Therefore, authors preparing communications for direct photographic reproduction are asked to take note of the new typing area of $6\frac{1}{4}$" x $9\frac{1}{2}$".

1961

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Tetrahedron Letters No. 1. pp. 1-4, 1961. Pergamon Press Ltd. Printed in United States of America.

CONFIRMATION OF THE TRICYCLO[6,2,0,$0^{3,6}$]-DECANE STRUCTURE FOR THE PHOTODIMER OF DIMETHYL 3-OXO-1,4-PENTADIENE-1,5-DICARBOXYLATE

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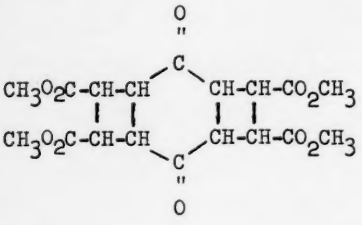
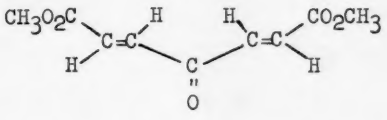
(Received 4 October 1960; in revised form 3 December 1960)

APPARENTLY the only suggested tricyclo[6,2,0,$0^{3,6}$]-decane derivative in the literature is tetramethyl tricyclo[6,2,0,$0^{3,6}$]-2,7-dioxodecane-4,5,9,10-tetracarboxylate (I). Stobbe and Färber[1] proposed the tricyclic-structure for the photodimer of dimethyl 3-oxo-1,4-pentadiene-1,5-dicarboxylate[2] (II) rather than the monocyclic dimer (III) on the basis of substitution by bromine rather than addition and the lower absorption maxima (not quantitatively measured).



(I)



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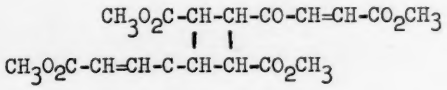

(III)

[1] H. Stobbe and E. Färber, Ber. 58, 1548 (1925).

[2] F. Straus, Ber. 37, 3297 (1904).

The tricyclic structure has not been accepted by standard reference works[3].

The proton magnetic resonance spectra of dilute solutions of the monomer and dimer[1,2] in trifluoroacetic acid containing approximately 1% tetramethylsilane (TMSi) as an internal reference were obtained at 60 Mc. using a Varian magnet and spectrometer. This solvent reference system has recently been used in a study of the spectra of amino acids and peptides[4]. In the conjugated olefinic region of the spectrum of (II) a single "nonequivalence" quartet occurs, the unsymmetrical doublets having shielding values of 2.50 and 2.95[5], and a 15.0 cycle splitting. Confirmation of the all-trans configuration of II[6] is provided by the presence of only one quartet and a typical trans value for the spin-spin coupling constant. The methoxyl resonance of II occurs at 5.99.

The NMR spectrum of the dimer shows a complete absence of protons attached to conjugated doubly-bonded carbon and thus excludes structure III, and corroborates structure I of Stobbe and Färber. A symmetrical

---

3 (a) Elsevier's Encyclopedia of Organic Chemistry, Edited by E. Josephy and F. Radt, Elsevier Publishing Co., Inc., Vol. 13, p. 6, New York, 1946. (b) A. M. Patterson and L. T. Capell, The Ring Index, Reinhold Publishing Co., New York, 1940. (c) R. A. Raphael, Chemistry of Carbon Compounds, Edited by E. H. Rodd, Vol. IIA, Chap. IX, Elsevier Publishing Co., New York, 1953.

4 F. A. Bovey and G. Tiers, J. Amer. Chem. Soc. 81, 2870 (1959).

5 All shielding values are given in ppm. in respect to the TMSi resonance taken as 10 ppm.

pair of incompletely resolved multiplets centered at 5.30 and 5.80 must arise from all the spin-coupled ring protons. This shape is fully consistent with two identical four-spin systems of the A_2B_2 type as required by I. A single methoxyl resonance, now located slightly up field at 6.09, shows the complete equivalence of all these groups as required by I, but not by III.

Because functional group shielding values have not been thoroughly established in trifluoroacetic acid, succinic anhydride was run in this solvent to obtain an approximate value for a proton on a carbon α and β to carboxyl groups. Its methylene resonance was found at 6.81. A further small reduction of a few tenths of a ppm. would be expected in going from a methylene to a methine proton and from the addition of a β-carbonyl group.

The reduction in the shielding of the ring protons of the dimer by more than one ppm. from the value for a proton on a carbon α and β to carbonyls must be due to the strong deshielding experienced by protons constrained to the plane of specially adjacent carbonyl groups. Jackman[7] has demonstrated this marked unshielding in the case of some diene dicarboxylic esters. A proton that is both cis to and β and γ to two carboxylate groups is 1.7 ppm. less shielded than when in the totally trans configuration. The magnitude of the reduction in shielding of the ring protons of the dimer may be explained if the four-membered rings are joined by trans fusions to the cyclohexanedione ring, since only in this case is each proton cis and β to two carbonyl

---

[6] Midorikawa, H., Bull. Chem. Soc. Japan 26, 302 (1953).

groups. It should be mentioned that for this interpretation to be correct, the protons α to the carbomethoxy groups on the same four-membered ring must be trans to each other and trans to the adjacent protons on the junction carbon atoms.

The ultraviolet absorption spectrum of I is typical of saturated cyclohexanones and shows no conjugation to be present. The infrared spectra are confirmatory of structure I for the dimer. Strong carbonyl stretching absorption occurs in KBr disk samples of the dimer at 1723 and 1758 cm^{-1} and of the monomer at 1685 and 1732 cm^{-1}. These values are about those expected[8] for structures I and II, the lower frequency arising from the keto and the higher from the ester group. Structure III, on the other hand, would show α,β-unsaturated keto and ester frequencies close to those of the monomer.

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[7] L. M. Jackman, Nuclear Magnetic Resonance Spectroscopy, Pergamon Press, London, 1959, p. 124.

[8] L. J. Bellamy, The Infra-red Spectra of Complex Molecules, Metheun and Co., Ltd., London, 2nd Ed., 1958, pp. 132,179.

Tetrahedron Letters No. 1, pp. 5-8, 1961. Pergamon Press Ltd. Printed in United States of America

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REACTIONS OF ETHYLENE-DI-ISOTHIOCYANATE WITH AMINES

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Institute of Organic Chemistry

University of Padova, Italy

(Received 28 November 1960)

PREVIOUSLY ethylene-di-isothiocyanate (I) has been shown to react with aniline giving the substituted ethylene-dithiourea (II; R^1=H R^2=C_6H_5);[1] analogous products have been obtained from $(CH_2)_4(NCS)_2$ with aniline, NH_3 and CH_3NH_2 [2] and from $(CH_2)_6(NCS)_2$ with $(CH_2)_2NH$.[3] We are studying the behaviour of I towards NH_3 and primary and secondary amines using various

$$\begin{array}{l} CH_2\text{-}NCS \\ | \\ CH_2\text{-}NCS \end{array} \quad (I) \quad + \quad \begin{array}{l} HNR^1R^2 \\ HNR^1R^2 \end{array} \longrightarrow \begin{array}{l} CH_2\text{-}NH\text{-}CS\text{-}NR^1R^2 \\ | \\ CH_2\text{-}NH\text{-}CS\text{-}NR^1R^2 \end{array} \quad (II) \qquad (1)$$

molecular ratios, and give here the results of some reactions made in water or aqueous medium, at room temperature. With dimethylamine and piperidine the substituted dithioureas are formed as primary products [II R^1=R^2=CH_3; R^1R^2=$(CH_2)_5$]; secondary products are formed in very small amounts and have not yet been fully identified.

In the reactions hitherto studied with primary amines - CH_3NH_2 and $C_2H_5NH_2$ - the substituted di-thioureas (II) have on the contrary been

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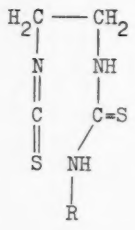
[1] A.Ya. Yakubovic and V.A. Klimova J.Chem. Soc. U.S.S.R. 9, 1777 (1939); Chem.Abstr. 34, 3685 (1940).

[2] J.v. Braun and G. Lemke Ber. 55, 3552 (1922).

[3] A.G. Bayer, Brit. Pat. 753,247; Chem. Abstr. 51, 9681 (1957).

obtained only as secondary products, even using excess of amine. The main products are originated, according to the analytical results, in a reaction of I with a sole molecule of amine; namely, with CH_3NH_2; A: m.p. 202-203° (Found: C, 34.10; H, 5.37; N, 23.96; S, 36.30. $C_5H_9N_3S_2$ requires C, 34.28; H, 5.18; N, 23.99; S, 36.54%); with $C_2H_5NH_2$; B: m.p. 166-167° (Found: N, 21.98; S, 34.00. $C_6H_{11}N_3S_2$ requires: N, 22.21; S, 33.84%).

Structures III to VI could be theoretically thought to fit with



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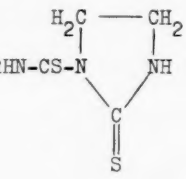

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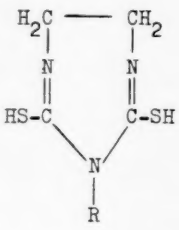

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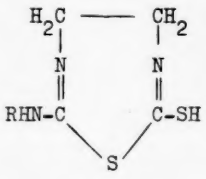
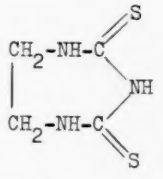


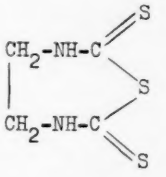
VI

the analytical figures of A and B.

III can be ruled out since the I.R. spectra of the compounds do not show the characteristic absorption of the isothiocyanate grouping in the



V'



VII

range of 2100 cm^{-1}.* Formula V' has been given to a compound obtained both from reaction of I with NH_3, and of the hypothetic ethylen-thiuram-monosulphide (VII) with NH_3 [4]; (in the latter reaction, the AA have also isolated II. $H_2O(R^1=R^2=H)$. Structure V is furthermore related to the 1,5 di- and 1,3,5-

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* We are indebted to Dr. C. Pecile and to the Institute of Physical Chemistry of the University of Padua for the I.R. spectra.

[4] G.D. Thorn and R.A. Ludwig, Canad.J.Chem. 32, 872 (1954).

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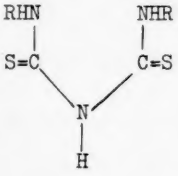
trialkyl-dithiobiurets (VIII) and less directly to the 1,2,4 triazolidine-3, 5-dithiones (IX); VI may be related to X, a structure given to the hydrolysis product of XI.[5] The structure given to VII is,



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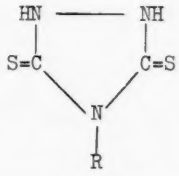
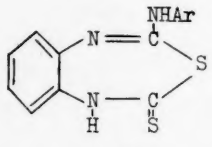
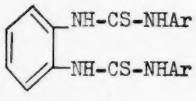


IX

on its side, related to 1,5-dimethyl-thiuram-monosulphide (XII)[6] and less directly to 1,3,4-thia-imidazolidine-2,5-dithiones (XIII). We assign to compounds A and B obtained from I with CH_3NH_2 and $C_2H_5NH_2$, the structures of 1-methyl- and 1-ethyl- thiocarbamyl-imidazolidine-2-thione (IVA and IVB)



X



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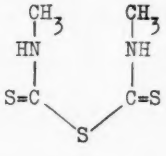
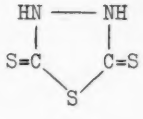
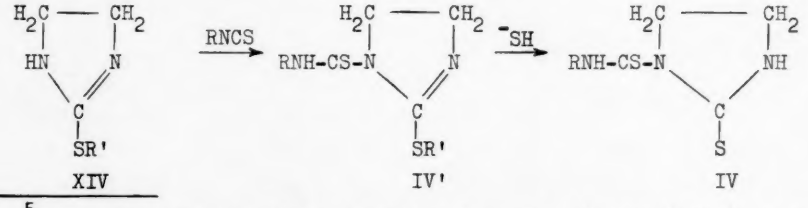


XII



XIII

because they are identical with the ones obtained, by purpose of comparison, following equation (2). The identity has been checked by m.p.s and mixed m.p.s, I.R. spectra, chromatographic behaviour (R_f and colour reactions with Grote's reagent and with $AgNO_3$), solubilities and other physical properties.



XIV IV' IV (2)

[5] T.N. Ghosh and P.C. Guha, J.Indian Chem.Soc. 6, 181 (1929); T.N. Ghosh, Ibid. 10, 583 (1933).

[6] F. D'Angeli and A. Iliceto Gazz.Chim.Ital. 89, 2095 (1959).

Reactions of equation (2) are an application of the synthesis of 1,5-di-alkyl-2,4-dithiobiurets (VIII) [7,8] which are the open chain analogs of structure IV; it seems unlikely that in the mild conditions in which both steps are performed (0° or room temperature) the five atom ring of 2-alkyl-mercapto-2-imidazoline (XIV) would undergo any transformation besides the expected 1-thio-carbamilation and subsequent thio-hydrolysis. Research is progressing to give further evidence to the permanence of such ring.

Both amidic nitrogens and the thiolic tautomeric sulphur of thioureas are known to fail to react with alkyl- or aryl-isothiocyanates;[7] should compound III be the first product of reaction between I and a single mole of a primary amine, its transformation into IV (or V and VI) would only be made possible by the favouring steric situation leading to a cycle; a different intermediate might in any case be involved.

Some of the properties previously described for 1,5-dimethyl-thiuram-monosulphide XII [6] and the evidence given here for the structure of compounds IVA and IVB offers some doubt as to whether the assigned seven membered ring structures[4] really belong to compounds V' and VII.

We gratefully acknowledge the support by Shell Internationale Research Maatschappij, N.V. The Hague, Holland, for the investigation.

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[7] F.H.S. Curd, D.G. Davey, D.N. Richardson and R. de B. Ashworth, J.Chem.Soc. 1739 (1949).

[8] A.E.S. Fairfull and D.A. Peak, J.Chem.Soc. 796 (1955).

Tetrahedron Letters No. 1, pp. 9-11, 1961. Pergamon Press Ltd. Printed in United States of America

1961

PHOSPHORORGANISCHE VERBINDUNGEN[1]

DARSTELLUNG UND EIGENSCHAFTEN α-SUBSTITUIERTER PHOSPHINOXYDE

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Aus dem Institut für Organische Chemie der Universität Mainz

(Received 29 November 1960)

IN vorangehenden Arbeiten wurde gezeigt, daß phosphorständige Methyl- und Methylengruppen in Phosphinoxyden und ähnlichen Verbindungen aciden, d.h. durch Basen abspaltbaren Wasserstoff enthalten.[2] In Fortsetzung dieser Arbeiten interssierte die Darstellung und Reaktionsfähigkeit α-substituierter Phosphinoxyde.

Diphenyl-α-chlorbenzyl-phosphinoxyd $(C_6H_5)_2P(O)\text{-}CHClC_6H_5$ ließ sich darstellen durch Einwirkung von t-Butylhypochlorit auf Diphenylbenzylphosphinoxyd in Eisessig in einer Ausbeute von 36% (Schmelzpunkt 231°).

Die anionoide Austauschbarkeit des Halogens in dieser Verbindung erwies sich als sehr gering. Die Verbindung wurde durch 16-stünd. Kochen mit Kaliumacetat-Eisessig ebensowenig verändert, wie durch alkoholische Silbernitrat-lösung.

Die analoge Brom-verbindung $(C_6H_5)_2P(O)\text{-}CHBrC_6H_5$ konnte durch längeres Kochen von Diphenylbenzylphosphinoxyd mit N-Brom-succinimid in Tetrachlorkohlenstoff dargestellt werden. Schmp. 204-206°. Das Halogen in dieser Verbindung ist deutlich positiviert . So trat z.B. beim Erhitzen mit Triphenylphosphin

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[1] XXIV.Mitteil.: Chem.Ber., z.Zt. im Druck.

[2] L. Horner u. Mitarbeiter, Chem.Ber. 91, 61 (1958) und 92, 2499 (1959).

in Ameisensäure eine Substitution des Broms durch ein Proton ein. Hierbei ist die Anwesenheit des Phosphins als Akzeptor für das positive Brom notwendig. Die Darstellung eines α-nitro-substituierten Phosphinoxyds gelang durch Umsetzung von mittels Kalium-tert.-butylat metalliertem Diphenylbenzylphosphinoxyd mit Äthylnitrat in Toluol unter Stickstoff bei einer Temperatur unter 0°.

$$(C_6H_5)_2\text{-P(O)-CHK-}C_6H_5 + C_2H_5ONO_2 \longrightarrow (C_6H_5)_2\text{-P(O)-CH(NO}_2)C_6H_5 + C_2H_5OK$$

Das in einer Ausbeute von 62% d.Th. erhaltene Produkt zersetzt sich bei 183-184°.

Die Nitroverbindung konnte in Gegenwart von Raney-Nickel bei Normaldruck und Zimmertemperatur katalytisch zur Aminoverbindung reduziert werden in einer Ausbeute von 50% d.Th. Das Diphenyl-α-aminobenzyl-phosphinoxyd $(C_6H_5)_2P(O)\text{-CH(NH}_2)C_6H_5$ schmilzt bei 132° unter Zersetzung. Die gleiche Verbindung kann analog dem für α-Aminophosphonsäureester angegebenen Verfahren[3] durch Kochen einer Lösung von diphenylphosphiniger Säure in Benzol mit Hydrobenzamid dargestellt werden.

Infolge der acidifizierenden Wirkung der Diphenylphosphinylgruppe kann die beschriebene Aminoverbindung durch Einwirkung von Natriumnitrit in saurer Lösung in eine Diazoverbindung überführt werden:

$$(C_6H_5)_2P(O)\text{-}\underset{\displaystyle NH_2}{\underset{|}{CH}}\text{-}C_6H_5 + HNO_2 \longrightarrow (C_6H_5)_2P(O)\text{-}\underset{\displaystyle N_2}{\underset{\|}{C}}\text{-}C_6H_5 + H_2O$$

Infolge der schlechten Abtrennbarkeit von gleichzeitig gebildetem α-Hydroxyphosphinoxyd konnte die Diazoverbindung bisher nicht in analysenreiner Form dargestellt werden. Das aus Chloroformlösung mit Petroläther

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[3] N. Kreutzkamp u. G. Cordes, Liebigs.Ann. 623, 103 (1959)

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ausgefällte, gelbrote Produkt zersetzt sich bei 155° und entwickelte mit Eisessig 80 % d.Th. an Stickstoff. Hierbei entstand α-Acetoxybenzyl-diphenylphosphinoxyd vom Schmelzpunkt 175°C.

Durch Umsetzung der Diazoverbindung mit einer benzolischen Bromwasserstoff-lösung bildete sich das eingangs beschriebene Diphenyl-α-brombenzylphosphinoxyd.

Bei der Behandlung mit wässrigen Säuren wandelt sich die Diazoverbindung quantitativ in das schon bekannte Diphenyl-α-hydroxybenzylphosphinoxyd um (Schmp. 176°).[4]

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[4] R.C. Miller, C.D. Miller, W. Rogers u. L.A.Hamilton, J.Amer.Chem.Soc. 79, 424 (1957).

Tetrahedron Letters No. 1, pp. 12-16. Pergamon Press Ltd. Printed in United States of America

PHOTOISOMERISIERUNGEN DER LUMICOLCHICINE UND DES COLCHICEINS

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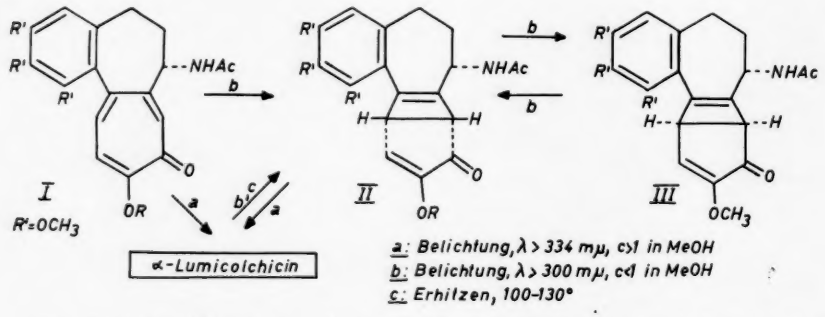
(Received 28 November 1960)

Colchicin (I, R=CH_3) wird in wässriger Lösung durch Sonnenlicht isomerisiert[1,2,3] zu α-Lumicolchicin, β-Lumicolchicin (II, R=CH_3) und γ-Lumicolchicin (III). Nach Forbes[4] und Gardner[5] kommen β- bzw. γ-Lumicolchicin stereoisomere tetracyclische Strukturen II bzw. III zu, deren absolute Konfigurationen wir unter Berücksichtigung der Arbeit von Hardegger[6] wie folgt wiedergeben:



Die Konstitution des α-Lumicolchicins war bisher unbekannt. Die

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1. R.Grewe, Naturwiss. 33, 187 (1946)
2. R.Grewe und W.Wulf, Chem.Ber. 84, 621 (1951)
3. F.Santavy, Coll.Czech.Chem.Comm. 16, 665 (1951)
4. E.J.Forbes, J.Chem.Soc. 1955, 3864
5. P.D.Gardner,R.L.Brandon und G.R.Haynes, J.Am.Chem.Soc. 79,6334 (1957)
6. H.Corrodi und E.Hardegger, Helv.Chim.Acta 38, 2030 (1955)

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Ausbeuten hieran sind sehr unterschiedlich: 31 %[2], 5 %[4] und 0 %[3,5] d.Th. Da über photochemische Umwandlungen der Lumicolchicine bisher nichts bekannt war, hielten wir als Erklärung der wechselnden Ausbeuten für wahrscheinlich, daß bereits entstandenes α-Lumicolchicin unter den verschiedenen Versuchsbedingungen jeweils anderweitig photochemisch verändert werden könnte. Da die Absorption des Colchicins gegenüber der des α- und besonders des β-Lumicolchicins stärker ins Langwellige verschoben ist, versuchten wir, durch Verwendung von Lichtfiltern etwaige photochemische Successivreaktionen[7] der Photoisomeren zu unterdrücken. Bei Bestrahlung von Colchicin mit Licht von $\lambda > 334$ mμ (Hg-Brenner H P K 125 W, Filterlösung No."9"[8], 266 Std., c = 3,8 in Methanol) erhielten wir neben 22 % II und 5 % III das α-Isomere mit einer Ausbeute von 52 % d.Th. (Fp. 164°, MG 312, ber. 399 in Dimethylsulfoxyd, $[\alpha]_{546}$ + 129° (Chlf.), λ_{max}^{MeOH} 330, 281, (227), 217 mμ). α-Lumicolchicin reagierte nicht mit Ketonreagenzien wie Hydroxylamin und Phenylhydrazin. Es ließ sich unter Normalbedingungen nicht hydrieren ($Pd/BaSO_4$ in Dioxan; PtO_2 in Dioxan, in Eisessig oder Eisessig/HCl).

Mit $NaBH_4$ in Methanol erhielten wir einen Alkohol IV, $C_{22}H_{27}NO_6$ (Fp. 284-286°, $[\alpha]_{546}$ - 300° (Chlf.), λ_{max}^{MeOH} 277, 227, (214) mμ); Monoacetat $C_{24}H_{29}NO_7$ (Fp. 172°, $[\alpha]_{546}$ - 243° (MeOH), λ_{max}^{MeOH} 278,226,(217) mμ). IV ließ sich ebensowenig hydrieren wie α-Lumicolchicin; mit CrO_3-Pyridin-Komplex wurde dieses regeneriert.

Während die aus II bzw. III mittels $NaBH_4$ dargestellten Alkohole[4] mit verdünnten Säuren unter Abspaltung von Methanol glatt zu Ketonen

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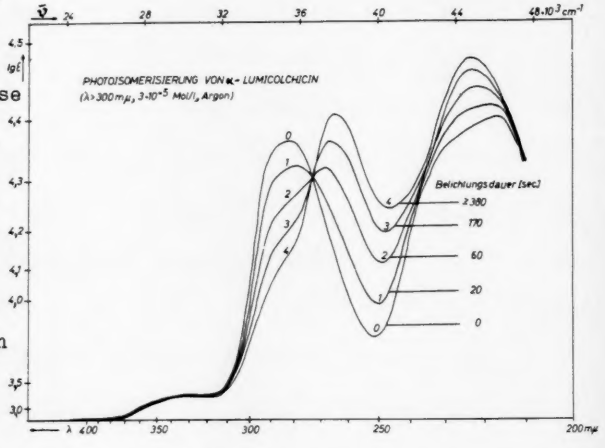
7. G.O.Schenck, O.-A.Neumüller und R.Koch, Strahlentherapie, im Druck

8. M.P.Rappoldt, Dissertation Leiden, 1958

hydrolysierten, blieb IV unter diesen Bedingungen unverändert. Hiernach kann die Methoxylgruppe des Ringes C bei α-Lumicolchicin und seinem Alkohol IV nicht mehr an einer Doppelbindung gebunden sein. IR- und NMR[9]-Spektren sind hiermit vereinbar.

Wir fanden ferner, daß α-Lumicolchicin bei Belichtung (λ>300 mμ) in verdünnter methanolischer Lösung (c<1) in ein "isosbestisches Gemisch" von β- und γ-Lumicolchicin überging (vgl. Abb.). Da II und III UV- und IR-spektroskopisch nicht unterschieden werden können, verfolgten wir diese photochemischen Successivreaktionen polarimetrisch. Dabei ergab sich, daß α-Lumicolchicin bis zur Erreichung des isosbestischen Gemisches in II überging.



Ueberraschenderweise führt die optische Anregung von II auch zu α-Lumicolchicin. Da jedoch das α-Isomere unter den Versuchsbedingungen ständig in das β-Isomere zurückverwandelt wird, verbleibt schließlich das isosbestische Gemisch von II und III. Bestrahlt man II jedoch in solchen Konzentrationen, in denen α-Lumicolchicin unlöslich ist, so fällt dieses schon während der Bestrahlung aus (Ausbeute 38 %) und entzieht sich so weiteren Umwandlungen.

Besonders charakteristisch für die enge Verwandtschaft ist die thermische Umwandlung von α-Lumicolchicin zu β-Lumicolchicin, die bei

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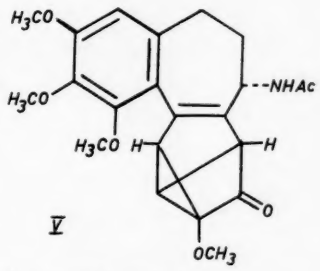
9. Wir danken Herrn Dr. E.G.Hoffmann für Messung und Diskussion der NMR-Spektren.

100-130° in Lösung oder in festem Zustand quantitativ verläuft. Die Reaktionen: α-Isomeres $\underset{\text{Licht}}{\overset{\text{Hitze}}{\rightleftharpoons}}$ β-Isomeres lassen sich in Parallele setzen zur thermisch reversiblen Photoisomerisierung der Norbornadiendicarbonsäure-(2.3) zur Quadricyclo[2.2.1.$0^{2.6}$.$0^{3.5}$]heptandicarbonsäure-(2.3)[10]. Dementsprechend lassen sich unsere bisherigen Befunde am besten durch die für α-Lumicolchicin von uns diskutierte Formel V (R=CH_3) erklären. Die photochemische Bildung der Lumicolchicine und ihre wechselseitigen photochemischen und thermischen Umwandlungen sind interessante Beispiele reiner Valenztautomerisierungen. Für diese Umwandlungen ist offenbar die Ketogruppe notwendig: IV erwies sich als photochemisch und thermisch stabil.



V

Eine Verbindung mit dem Grundgerüst des Tricyclo[2.2.1.$0^{2.7}$]heptans (VI)[11] war früher von Wagner-Jauregg[12] diskutiert, später jedoch von Meinwald[13] als Pentalanderivat aufgeklärt worden.

VI

Auch Colchicein (I, R=H), von Santavy[3] als photostabil beschrieben, wird photoisomerisiert. Bisher isolierten wir "Lumicolchicein A" (Fp. 236-240°, $[\alpha]_{546}$ - 236° (Chlf.), λ_{max}^{MeOH} 276, 227 mμ), das mit Diazomethan α-Lumicolchicin lieferte und das sich gegen katalytische Hydrierung als ebenso inert erwies wie IV und V. Ferner erhielten wir "Lumicolchicein B" (Fp. 147°, $[\alpha]_{546}$ + 189° (Chlf.), λ_{max}^{MeOH} 339,267,224 mμ), dessen Dioxim (Fp. 186°) mit einem aus β-Lumicolchicin unter Abspaltung

10. S.J.Cristol und R.L.Snell, J.Am.Chem.Soc. 80, 1950 (1958)
11. von A.S.Dreiding in einer Privatmitteilung als "Trisequan" bezeichnet
12. R.Griot und T.Wagner-Jauregg, Helv.Chim.Acta 41, 867 (1958)
13. J.Meinwald, Proc.Chem.Soc. 1958, 286

der Methoxylgruppe bereiteten Dioxim[4] identisch war.

Nach den chemischen Befunden und in Einklang mit Molrotationsdifferenzen und IR-Spektren besitzt demnach Lumicolchicein B die Konstitution II (R=H). Sinngemäß ist für Lumicolchicein A die Formel V (R=H) abzuleiten.

Der Firma CIBA danken wir für Colchicin.

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ZUR STRUKTUR VON $NiC_{10}H_{12}$ UND $PdC_{11}H_{14}$

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Anorganisch-chemisches Institut der Universität München

(Received 6 December 1960)

DURCH Umsetzung von $Ni(CO)_4$ mit freiem Cyclopentadien hatten wir eine leicht flüchtige, rote Verbindung der Zusammensetzung $NiC_{10}H_{12}$ erhalten, für die wir die Struktur eines Nickel(0)-di-cyclopentadiens vorschlugen.[1] Der gefundene Diamagnetismus, das schwache Dipolmoment und auch das IR-Spektrum waren durchaus damit verträglich. Wir wiesen bereits in unserer ersten Mitteilung darauf hin, daß im IR-Spektrum zum Teil sehr intensive Banden beobachtet wurden, die genau den im $Ni(C_5H_5)_2$[2] gefundenen entsprachen.

Des weiteren haben wir bereits früher Pd-Verbindungen beschrieben, die von cyclischen 1,3-Dienen ausgehend erhalten worden waren und deshalb zunächst als π-Komplexe dieser Olefine angesehen wurden.[3] Eine Überprüfung der vorgeschlagenen Strukturen zweier typischer Verbindungen mittels NMR-Messungen gestattet uns nun, eine wesentlich exaktere Aussage zum Strukturproblem zu machen. Die wichtigsten Ergebnisse dieser Untersuchungen seien im folgenden kurz zusammengefasst.[4]

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[1] E.O. Fischer und H. Werner, Chem.Ber. 92, 1423 (1959).

[2] H.P. Fritz, Chem.Ber. 92, 780 (1959).

[3] E.O. Fischer und H. Werner, Chem.Ber. 93, 2075 (1960).

[4] Für die Durchführung dieser Messungen und die wertvollen Anregungen für ihre Auswertung möchten wir Herr Dr. W. Brügel, Badische Anilin- & Soda-Fabrik, Ludwigshafen, unseren herzlichsten Dank aussprechen.

Die Messungen wurden bei einer Arbeitsfrequenz von 40 MHz an Lösungen der Komplexe in Benzol, Cyclohexan oder Aceton durchgeführt.[5] $PdC_{11}H_{14}$, "Cyclohexadien-(1,3)-cyclopentadien-Palladium(0)", wurde gegen Wasser als äußeren Standard, $NiC_{10}H_{12}$ gegen Tetramethylsilan als inneren vermessen. Dabei wurden die in Tabellen 1 und 2 angegebenen "chemical shifts" und Intensitäten beobachtet.

Tabelle 1 "Chemical shifts", Intensitäten und Zuordnungen für $PdC_{11}H_{14}$.

"Chemical shifts" (in Hz)			
in C_6H_6	-27	+20	+148
in C_6H_{12}	-32	-1+4	
in Aceton	-20	+11+15	+154
Intensitäts-verhältnis	5 :	3 :	6
Zuordnung nach Abb.1	H_C	H_A	H_B

Tabelle 2. "Chemical shifts", Intensitäten und Zuordnungen für $NiC_{10}H_{12}$

"Chemical shifts" (in Hz)				
in C_6H_6	+31	+37	+83.5	+199
	4.72	4.87	6.04	8.93
Int.-Verh.	5 :	1 :	2 :	4
Zuordnung nach Abb.2	H_C	H_X	H_A	H_B

[5] Eine eingehendere Behandlung dieser Untersuchungen erscheint an anderer Stelle.

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$PdC_{11}H_{14}$ zeigt insgesamt drei deutliche Signale, die im angegebenen Intensitätsverhältnis stehen. Die etwas unterschiedliche Lage in den drei Medien ist durch Lösungsmittel-Einflüsse bedingt. Das sehr ausgeprägte Signal im negativen Bereich entspricht unzweifelhaft den fünf chemisch gleichwertigen Protonen des Cyclopentadienyl-Systems, das etwas breitere

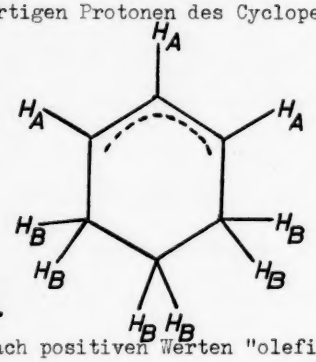

ABB. 1.

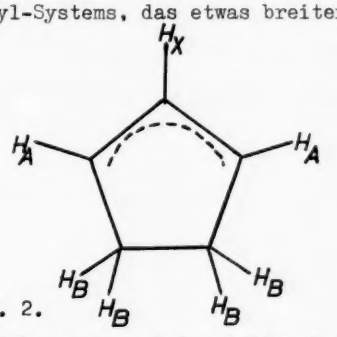

ABB. 2.

bei schwach positiven Werten "olefinischen" Protonen und das dritte bei etwa 150 Hz schließlich Protonen in "cyclischen" Methylen-Gruppen.[6] In Verbindung mit den gefundenen Intensitätsverhältnissen ist also eindeutig eine Struktur als Cyclohexenyl-Palladium-Cyclopentadienyl anzunehmen, wie sie durch Abb.3 veranschaulicht sei.

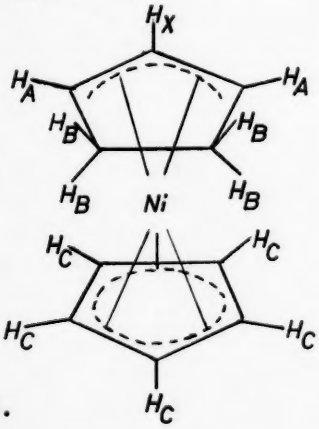

ABB. 3.

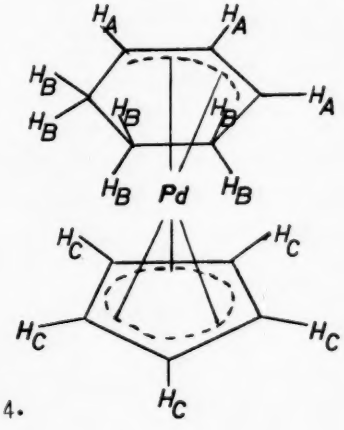

ABB. 4.

[6] vgl. L.H. Meyer, A. Seika und H.S. Gutowsky, J.Amer.Chem.Soc. 75, 4567 (1953).

Für das $NiC_{10}H_{12}$, an das sich hinsichtlich des NMR-Spektrums die vom Methylcyclopentadien dargestellte analoge Verbindung, $NiC_{12}H_{16}$, eng anschließt, finden sich die in Tabelle 2 angeführten Werte. Auch hier lassen sich die "chemical shifts" den vier erwarteten Protonenarten zuordnen. Die Intensitäten stehen in den zu fordernden Verhältnissen. Somit ergibt sich auch hier eine "en-yl"-Struktur des Komplexes als Cyclopentadienyl-Nickel-Cyclopentenyl entsprechend Abb.4.

Eine kürzlich erfolgte Überprüfung der IR-Spektren dieser Verbindungen[7] bestätigt die NMR-Befunde aufs Beste und die UV-Spektren etwa von $C_5H_5PdC_3H_5$[8] und $C_5H_5PdC_6H_9$ zeigen eine weitgehende Analogie der Systeme an.

Weitere Untersuchungen dieser erstmals in Ringen gefundenen "en-yl"-Strukturen sind im Gang.

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[7] H.P. Fritz, Chem.Ber. im Erscheinen.

[8] B.L. Shaw, Proc.Chem.Soc. 247, (1960).

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1961

A DIMER OF CYCLOBUTADIENE

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Elise Marica and C. D. Nenitzescu
Chemical Institute of the Academy of R.P.R., Bucharest

(Received 13 December 1960)

IN this communication a preliminary report is presented concerning a dimer of cyclobutadiene, formed in the decomposition of the previously described $C_4H_4 \cdot AgNO_3$ complex. [1]

As it was shown, [1] on treatment of this complex with water, a volatile compound is evolved with the elementary composition C_1H_1. If the decomposition of the silver nitrate complex is carried out with an aqueous solution of sodium chloride in the presence of an organic solvent, solutions of the decomposition product are obtained. The gas-chromatogram of the ethereal solution thus prepared reveals the presence of only one component, in the range corresponding to a C_8 hydrocarbon.

A solution in ethyl chloride obtained as indicated above, leaves after evaporation of the solvent a colourless liquid which was analysed mass-spectrometrically. The

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[1] M. Avram, E. Marica and C. D. Nenitzescu, Chem.Ber. 92, 1088 (1959).

mass-spectrogram thus obtained is identical with the mass-spectrogram of the volatile compound evolved in the thermal dissociation of the complex $C_4H_4 \cdot AgNO_3$ heated under vacuum. Ionizing tensions of 2o and 4o volts were employed. A principal peak of mass number (MN) 1o4 is observed, together with a smaller peak of MN 1o3 and an isotopic peak of MN 1o5. Besides these, the only other important peaks have MN 52 and 51, accompanied by smaller peaks with MN 53 and 5o. At ionizing tensions of 4o volts or more, the intensities of peaks 51 and 52 are about the same as of peak 1o4, while at 2o volts ionizing tension, peak 52 is about 1oo times smaller than peak 1o4. The conclusion emerges that the compound obtained from the $C_4H_4 \cdot AgNO_3$ complex is a C_8H_8 hydrocarbon which under electron impact undergoes, besides the usual hydrogen splittings, a breakdown into C_4H_4 molecules, and that this breakdown is definitely favoured over other possible breaking modes.

The infrared absorption spectrum of the C_8H_8 compound was then determined in CS_2 (66o-133o cm^{-1}) and CCl_4 solution (133o-181o ; 226o-33oo cm^{-1}). A table of band maxima is appended. The IR spectrum was also determined of the C_8H_8 in gaseous state, by decomposition of the $C_4H_4 \cdot AgNO_3$ complex with a sodium chloride solution in heavy water, in an evacuated cell. The vapour spectrum differs from the solution spectrum through small shifts due to the change

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Infra-red frequencies of C_8H_8 in solution
(CS_2 660-1330 cm^{-1} ; CCl_4 1330-3300 cm^{-1})

3094	(M)	C - H stretching
3033	(S)	
2975	(VS)	
2967	(VS)	
1710	(VW)	
1700	(VW)	
1640	(W)	
(1550)	(W)	C = C stretching (in gas only)
1305	(W)	
1288	(S)	C - H deformation
1208	(W)	
1190	(W)	
1164	(M)	C - C stretching
1152	(M)	
1050	(W)	
990	(W)	
966		
957	(M)	C_4 ring deformation
915		
912	(W)	
890	(W)	
880	(W)	
820	(M)	C - H deformation
810	(M)	
792	(S)	
775	(W)	
745	(M)	
732	(M)	

(W) weak, (M) medium, (S) strong and (VS) very strong bands. The relative intensities only were estimated.

in aggregation state (ca. 1o cm^{-1}), through the appearance of a weak band at 155o cm^{-1} which cannot be seen in the solution spectrum (in this region CCl_4 presents itself absorption), through fine structure of the 8oo cm^{-1} band in the vapour spectrum (78o-83o cm^{-1}), and through the splitting in two of the 735 cm^{-1} band in the solution spectrum.

The IR spectrum is relatively simple and agrees with a provisionally proposed structure of a tricyclooctadiene (I) for the C_8H_8 compound. Unsaturated character is manifested in the presence of CH stretching bands at 3o94 and 3o33 cm^{-1}. The double band at 2967-2975 cm^{-1} is probably due to CH stretching of the saturated central ring in (I), with a displacement towards higher frequencies owing to ring strain. A band, similar in position (297o cm^{-1}) and intensity was found also in the tricyclic dimer of benzocyclobutadiene [2] (II). In the low frequency region there appear deformation vibrations of saturated and olefinic C-H bonds. The intense band at 1288 cm^{-1} can be assigned to the deformation vibration of the C-H bond in the saturated ring, and the band at 957 cm^{-1} is probably due to the deformation vibration of the four-membered saturated rings. The 155o cm^{-1} band in the vapour spectrum is undoubtedly a C=C stretching vibration of double bonds in the side-rings. A band at 1566 cm^{-1} has been found in the cyclobutene spectrum. [3]

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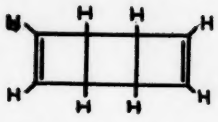
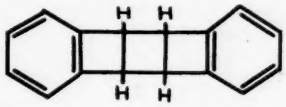
[2] M. Avram, D. Dinu and C.D. Nenitzescu, Chemistry and Industry 1959, 257.

[3] R. C. Lord and D. G. Rea, J.Amer.Chem.Soc. 79, 24o1 (1957).



(I)



(II)

(III)

(IV)

The proposed structure (I) involves a dimerization of cyclobutadiene through cycloaddition, similarly with the dimerizations observed with benzocyclobutadiene, [2] tetramethylcyclobutadiene, [4] and 1,3-diphenylcyclobutadiene. [5]

From the two possible configurations (III) and (IV), the trans-structure (IV) with C_{2h} symmetry is more probable on symmetry grounds.

The ethereal solution of the C_8H_8 dimer yields on treatment with silver nitrate solution a $C_4H_4 \cdot AgNO_3$ complex, identical in every respect, IR spectrum included, with the initial $C_4H_4 \cdot AgNO_3$ complex. In a detailed analysis of the IR spectrum of this silver nitrate complex, Fritz, McOmie and Sheppard have shown [6] that the spectrum provides support for a monomeric formulation $C_4H_4 \cdot Ag\,NO_3$,

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[4] R. Criegee and G. Louis, Chem. Ber. 90, 417 (1957) R. Criegee, G. Schröder, G. Maier and H. G. Fischer, Chem. Ber. 93, 1553 (1960).

[5] E. H. White and H. C. Dunathan, Amer.chem.Soc. Meeting Chicago, Sept. 1958, Abstracts p. 41 P ; cited after E. Vogel, Angew. Chem. 72, 4 (1960).

[6] H. P. Fritz, J. F. W. McOmie and N. Sheppard, Tetrahedron Letters 1960, under print.

involving C_4H_4 units as hydrocarbon ligands. This means that when the silver-nitrate complex is formed from the dimer, a dissociation $C_8H_8 \longrightarrow 2\ C_4H_4$ must take place. Although inusual, such a hypothesis would not be altogether excluded because breakage of single bonds on complexation of olefinic ligands with metals was observed in some cases. [7, 8] Also, considerable stabilization for cyclobutadiene on complexation with metals may be anticipated. Attempts to solve this problem chemically, with larger amounts of substance, are under way.

The mass-spectrometric determinations were performed by Professor N. Martalogu and Miss D. Mumuianu from the Institute of Atomic Physics, Bucharest, to whom our best thanks are given. We also are particularly grateful to Dr. J. F. W. McOmie, Dr. N. Sheppard and Dr. H. Fritz for discussions.

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[7] R. B. King and F. G. A. Stone, J.Amer.chem.Soc. 82, 4557 (1960).

[8] B. F. Hallam and L. P. Pauson, J. 1958, 646.

Tetrahedron Letters No. 1, pp. 27-31, 1961. Pergamon Press Ltd. Printed in United States of America

1961

EQUILIBRIUM ISOMERIZATION OF METHYLENECYCLOBUTANE AND 1-METHYLCYCLOBUTENE

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(Received 20 December 1960)

THE relative stability at 250° of cyclic olefins, having a five- or a six-membered ring, has been the object of a recent communication[1] from this laboratory. We wish now to report on the equilibrium isomerization of methylenecyclobutane (I) and 1-methylcyclobutene (II).

It has been recognized[2] that, as for higher ring homologs,(II) is more stable than (I). Recently the heat of isomerization at 25° (ΔH° (exo → endo) ≈ -0.9 kcal/mole) has been calculated[3] from the heats of hydrogenation of the two olefins. However no direct measurement of the equilibrium has been reported.

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[1] E. Gil-Av and J. Shabtai, Chem. & Ind. 1630 (1960).

[2] P. Riesz, R.W. Taft, Jr. and R.H. Boyd, J. Amer. Chem. Soc. 79, 3724 (1957).

[3] R.B. Turner, in Theoretical Organic Chemistry, IUPAC Kekule Symposium. p. 79. Butterworths Scientific Publications, London (1959).

Since according to the literature,[4] the compounds studied tend to rearrange and to polymerize in acid conditions, a basic catalyst was tried for equilibration.

Rapid isomerization at room temperature without any side reactions was indeed found to take place with finely divided sodium on alumina.[5] Cripps and coworkers[6] have recently reported that, similarly, methylenecyclobutane-2,3-dicarboxylic acid anhydride readily rearranges to the endo-olefinic isomer in basic conditions, whereas no shift of the double bond occurs in acid solution.

(I) was prepared according to Roberts and Sauer[7] and after distillation was found to be 92.5% pure, the remainder consisting of about 3% 2-methyl-1-butene and 4-5% spiropentane. In a typical experiment 12.5 ml of (I) was stirred in a thermostat kept at 25° with 6 g of catalyst, prepared in situ by adding 1 g of sodium to 5 g of alumina[4] (Alcoa, Grade F, 100 mesh). Samples were taken every 30 min and analyzed by gas-

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[4] W. Shand, Jr., V. Schomaker, and J.R. Fischer, J. Amer. Chem. Soc. 66, 636 (1944).

[5] High Surface Sodium on Inert Solids , U.S. Industrial Chemicals Co., 120 Boradway, New York, N.Y.

[6] H.N. Cripps, J.K. Williams, V. Tullio and W.H. Sharkey, J. Amer. Chem. Soc. 81, 4904 (1959).

[7] J.D. Roberts and C.W. Sauer, ibid. 71, 3925 (1949).

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liquid chromatography, using silver nitrate/glycol as the stationary phase.[8] Total equilibration time was about two hours, with constant composition being reached already after 60 min. The peak area of (II) had to be corrected for 2-methyl-2-butene (III), which has the same retention volume as (II), and is formed in the experimental conditions from the less stable 2-methyl-1-butene (IV) present in the starting material. The maximum amount of (III) produced can be calculated from the residual concentration of (IV) by multiplying with the equilibrium ratio of (III) to (IV), which was found to be equal to 5.65 at 25°, in accord with thermodynamic data.[9] The correction does not however amount to more than 0.7% on the final figure.

Three separate experiments were carried out starting with (I), and the concentration of the exo and endo isomers were found to amount on the average to 85% and 15%, respectively, with an estimated error of ±1%.

The position of the quilibrium was confirmed by approach from (II). The endo isomer was prepared by fractionating the equilibrium mixture obtained from (I) on a spinning band column in the presence of sodium catalyst, added to effect continuous isomerization of the less volatile (I) accumulating

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[8] E. Gil-Av, J. Herling and J. Shabtai, J. Chromatog. 1, 508 (1958); J. Shabtai, J. Herling and E. Gil-Av, ibid., 2, 406 (1959).

[9] J.E. Kilpatrick, E.J. Prosen, K.S. Pitzer and F.D. Rossini, J. Res. Natl. Bur. Standards 36, 559 (1946).

in the still. The distillate (II) was accompanied by only 5% of (I); 4% of (IV) was also present, but the higher boiling (III) and spiropentane were absent.

Isomerization of (II) in identical conditions as above gave 86% of the endocyclic and 14% of the exocyclic olefin at equilibrium.

The free energy of isomerization (exo→endo) was calculated from the average value of the equilibrium constant: $\Delta F = -1.05$ kcal/mole.

Recently the relative stability at 25° of methylenecycloalkanes and 1-methylcycloalkenes, with 5 to 10 carbon atoms in the ring, has been determined.[10] It has been found that the equilibrium concentration for the exo isomer has a maximum value for the seven-membered ring compound (1.3%), decreases to 0.4% for methylenecyclohexane, and further to 0.09% for methylenecyclopentane.[11] The high value found for methylenecyclobutane is explained by a relatively large strain in (II) caused by the introduction of a second triagonal carbon into the four membered ring.[3]

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[10] A.C. Cope, D. Ambros, E. Ciganek, C.F. Howell and Z. Jacura, J. Amer. Chem. Soc. 82, 1750 (1960).

[11] Determined in acetic acid containing 0.25% p-toluenesulfonic acid; practically the same results were obtained with sodium/alumina as the catalyst.[12]

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It is noteworthy that isomerization of (I) over sodium/alumina makes 1-methylcyclobutene readily available and gives a purer product than the procedures used hitherto.[2,6]

Equilibration of five- and six-membered cyclo-olefins in the same experimental conditions as above, gives all the isomeric endocyclic olefins.[12] The only indication for the possible presence of the unknown 3-methylcyclobutene, in the experiments reported here, was the appearance of a small peak, corresponding to about 0.1%, which however was not identified. A coincidence of the peak for this additional isomer with that of another component is unlikely in view of the influence of structure on the retention volume of cyclic olefins over silver nitrate/glycol.[7]

The authors wish to thank Mr. Ch. Greener for the synthesis of methylenecyclobutane and Mr. D. Nurok for valuable assistance in the preparation of 1-methylcyclobutene.

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[12] E. Gil-Av and J. Herling, unpublished results.

Tetrahedron Letters No. 1, pp. 32-33, 1961. Pergamon Press Ltd. Printed in United States of America

BROMINATION OF PYRIDINE-N-OXIDE

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Wageningen, The Netherlands

(Received 20 December 1960)

The reactivity of pyridine-N-oxide towards electrophilic reagents has been investigated extensively. It has been found that when pyridine-N-oxide is heated with a mixture of fuming nitric acid and sulphuric acid at 90° for 1 h 4-nitropyridine-N-oxide is formed in a high yield[1]. The mercuration also proceeds smoothly: heating of the N-oxide with mercuric acetate in acetic acid solution for 2 hrs at 130° produces a reaction mixture containing derivatives substituted in positions 2 and 6[2]. Sulphonation only occurs under extreme conditions; it leads to the formation of pyridine-3-sulphonic acid[3]. The halogenation, however, has not yet been accomplished, as far as we know.

Several years ago we have found that pyridine-N-oxide was not brominated when it was heated with bromine for several hours above

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[1] a. E. Ochiai, K. Arima and M. Ishikawa, J. Pharm. Soc. Japan 63, 79 (1943); Chem. Abstr. 45, 5151 (1951).
b. H.J. den Hertog and J. Overhoff, Rec. Trav. Chim. 69, 468 (1950).

[2] M. van Ammers and H.J. den Hertog, Rec. Trav. Chim. 77, 340 (1958).

[3] a. H.S. Mosher and F.J. Welch, J. Am. Chem. Soc. 77, 2902 (1955).
b. M. van Ammers and H.J. den Hertog, Rec. Trav. Chim. 78, 586 (1959).

1961

100° in the presence of various metallic bromides as a catalyst[4]. We now treated the N-oxide with bromine at more elevated temperatures using sulphuric acid as a solvent in order to prevent deoxydation. Even when pyridine-N-oxide was heated with an excess of bromine in sulphuric acid for 20 hrs at 200°, no reaction occurred. Application of a method of bromination given by Derbyshire and Waters i.e. the use of a mixture of bromine, 90% aqueous sulphuric acid and silver sulphate which contains a high concentration of bromine cations, proved to be successful. The rate of the bromination according to this procedure at 150° is still very low, but when the heating is carried out at 200° for 20 hrs a mixture of bromopyridine-N-oxides is formed in a yield of about 10%.

The composition of the reaction product was established by reducing the N-oxides with iron powder and acetic acid and separating the bromopyridines formed by gas chromatography over a column filled up with 20% tritolylphosphate on chromosorb, using hydrogen as a carrier gas. It appeared that a mixture of 2- and 4-bromopyridine-N-oxide was formed in a ratio of about 1 : 2.

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[4] Cf. also the paper cited in note 3a.

[5] Cf. D.H. Derbyshire and W.A. Waters, J. Chem. Soc. 1950, 573.

Tetrahedron Letters No. 1, pp. 34-38, 1961. Pergamon Press Ltd. Printed in United States of America

A NOVEL APPROACH TO A KEY INTERMEDIATE IN THE TOTAL SYNTHESIS OF α-ONOCERIN

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(Received 20 December 1960)

The total synthesis of the naturally occurring triterpene α-onocerin was first accomplished by Stork and co-workers[3] via the coupling of the hydroxyketo acid(11). We wish to report here an alternate independent synthesis of this key intermediate.

The keto benzoate(1)[4] was converted to the hydroxyketone(2) in 96% yield following the method of Sondheimer[4]. The ketone ketal(3), m.p. 126.5-128°(C,71.29%; H,9.46%) was obtained in 58% yield by first ketalization of the hydroxy ketone(2) with ethylene glycol and then oxidation of the resulting hydroxy ketal with chromic acid in acetone[5]. The conversion of the ketone ketal(3) to the α-isopropoxymethylene derivative(4), m.p.

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[1] Sun Oil Company Fellow, 1959-60.

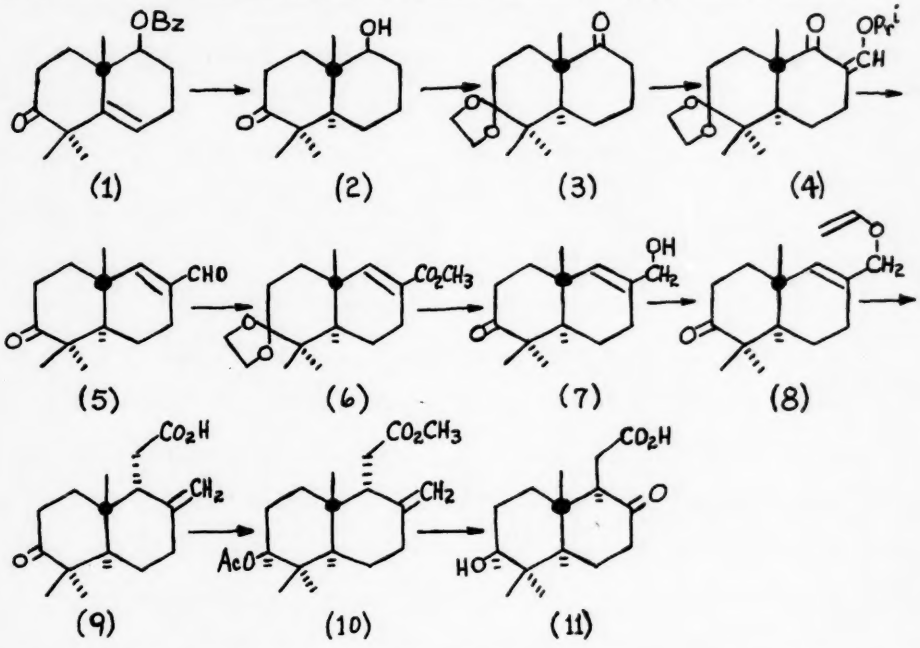
[2] Public Health Service Research Fellow of the National Heart Institute.

[3] G. Stork, J. E. Davies and A. Meisels, J. Amer. Chem. Soc. 81, 5516 (1959).

[4] F. Sondheimer and D. Elad, J. Amer. Chem. Soc. 79, 5542 (1957); 80, 1967 (1958).

[5] C. Djerassi, R. R. Engle and A. Bowers, J. Org. Chem. 21, 1547 (1957).

85-86°(C,70.85%; H,9.42%) was accomplished in 85% yield via the α-hydroxymethylene ketone ketal, m.p. 132-133°(C,68.59%; H,8.56%) and isopropylation by the method of Johnson and Posvic[6]. Reduction with sodium borohydride and treatment of the resulting alcohol, m.p. 124-126°(C,70.38%; H,9.94%) with aqueous mineral acid[7] resulted in the formation of the keto aldehyde(5), which without



further purification was oxidized with silver oxide to the corresponding acid, m.p. 202-204°(C,71.38%; H,8.60%) in 62% overall yield. Esterification with diazomethane and ketalization with

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[6] W. S. Johnson and H. Posvic, J. Amer. Chem. Soc. 69, 1361 (1947).

[7] P. Seifert and H. Schinz, Helv. Chim. Acta 34, 728 (1951).

ethylene glycol afforded a 93% yield of the ketal ester(6) m.p. 71-73°(C,69.30%; H,8.97%). The keto alcohol(7), m.p. 65-66°(C, 75.78%; H,9.93%) was then readily available in 84% yield [41% overall yield from the ketone ketal(3)] by reduction with lithium aluminum hydride and then treatment with 3 N aqueous hydrochloric acid.

Further modification of the keto alcohol(7) proceeded by equilibration[8] with ethyl vinyl ether to form the vinyl ether(8). Pyrolysis[9] of this oily vinyl ether afforded a 53% overall yield of the corresponding aldehyde, m.p. 76-79°(C,77.32%; H,9.72%) which was oxidized with silver oxide in 85% yield to the acid(9), m.p. 143-145°(C,72.75%; H,9.03%).

In order to ascertain the configuration of the newly-introduced acetic acid residue, the keto acid(9) was reduced by the Wolff-Kishner method in 91% yield to the 3-desoxyacid(9) m.p. 147-148°(C,76.67%; H,10.37%). This same acid was also prepared independently from the keto benzoate(1). Thus following the method of Sondheimer[4] the keto benzoate(1) was transformed to 5,5,9-trimethyl-trans-decalone-1. The α-n-butylthiomethylene derivative, m.p. 68-69°(C,73.38%; H,10.17%; S,10.62%) of this ketone was then prepared in 92% yield by the method of Ireland and Marshall[10]. On reduction with sodium borohydride and then

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[8] W. H. Watenabe and L. E. Conlon, J. Amer. Chem. Soc. 79, 2828 (1957).

[9] A. W. Burgstahler and I. C. Nordin, J. Amer. Chem. Soc. 81, 3151 (1959).

[10] R. E. Ireland and J. A. Marshall, J. Amer. Chem. Soc. 81, 6336 (1959).

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steam distillation from 2% aqueous sulfuric acid, the thiomethylene derivative afforded a 77% yield of the 3-desoxyaldehyde(5) [semicarbazone, m.p. 224-226°(C,68.56%; H,9.36%; N,16.09%)]. Further reduction with sodium borohydride afforded the corresponding allylic alcohol, b.p. 115-116°/0.8 mm.(C,80.56%; H,11.50%) in 91% yield. When this alcohol was equilibrated with ethyl vinyl ether[8] and the resulting vinyl ether pyrolyzed[9] directly, there resulted a 72% yield of the 3-desoxyaldehyde, m.p. 37-38° (C,81.89%; H,11.21%). Oxidation of this aldehyde with silver oxide then afforded a 91% yield of the 3-desoxyacid(9)[42% overall yield from the starting decalone].

In order to determine the configuration of the acetic acid side-chain, the 3-desoxyacid(9) was converted to the corresponding keto acid, m.p. 136-138°(C,71.29%; H,9.65%) in 82% yield with ozone. Formation of the enol-lactone, m.p. 91-92°(C,77.00%; H, 9.54%) in 55% yield with acetic anhydride-sodium acetate followed by methanolysis with sodium methoxide afforded a keto ester, m.p. 63-64)(C,72.17%; H,9.90%) in 73% yield. This latter ester was different (mixture m.p. 41-53°) from the ester, m.p. 71-72°(C, 72.23%; H,9.91%) obtained from the original keto acid directly with diazomethane. By virtue of its formation under basic conditions the 64°-keto ester is assigned the β-oriented (equatorial) acetate side-chain, while the acids related to the 72°-keto ester possess an α-oriented (axial) acetic acid residue.

In order to obtain the desired β-configuration of the side-chain in the 3-oxygenated series, the acid(9) was converted in

69% yield to the acetoxy ester(10), m.p. 121-122°(C,70.67%; H, 9.33%) by successive treatment with diazomethane, sodium borohydride and then acetic anhydride-pyridine. Ozonization and alkaline hydrolysis of the resulting keto ester, afforded the acid (11) m.p. 185-187° in 51% yield. This acid was identical [mixture m.p., infra-red] to that previously prepared by Stork and co-workers[3] and thus provides the link between the present work and the previously successful total synthesis of α-onocerin.

Acknowledgement: The authors' acknowledge the support of the Research Corporation and are grateful to Prof. Stork and Dr. Meisels for providing a sample of the acid(11).

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E R R A T U M

TETSUO NOZOE and HITOSHI TAKESHITA, Cuparene and cuprenene,

Tetrahedron Letters No. 23, 14-17 (1960)

The authors regret a mistyping which appeared in the above communication. p. 15, 18th line: for "$C_{10}H_{26}O_2$" read "$C_{10}H_{16}O_2$".

Tetrahedron Letters No. 2, pp. 41-42, 1961. Pergamon Press, Inc. Printed in the United States of America.

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HYDROGEN EXCHANGE OF FERROCENE AND ITS DERIVATIVES *

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Academy of Sciences, Moscow

(Received 2 January 1961)

FOLLOWING a short communication[1] referring to an unpublished observation by J.O. Santer on deuteration of ferrocene in the presence of $BF_3.D_2O$, we deem it necessary to report on our investigation of hydrogen exchange of ferrocene and its derivatives in acidic media.

We found ferrocene to substitute deuterium readily for hydrogen atoms when dissolved in anhydrous deuterosulphuric acid. At the same time ferrocene was oxidized to ferrocinium cation which, however, did not take part in hydrogen exchange. Both concurrent reactions, deuteroexchange and oxidation, proceeded at different rates.

Different acidic donors of deuterium with no oxidative properties smoothly exchange hydrogen in ferrocene. Thus the isotope exchange reaction of ferrocene hydrogen runs at room temperature in such media as a

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* Translated by A.L. Pumpiansky, Moscow

1 T.J. Curphey, J.O. Santer, M. Rosenblum and J.H. Richards, J.Amer.Chem.Soc. 82, 5249 (1960).

mixture of deuteroacetic and trichloroacetic acid, deuterophosphoric acid in dioxane solution, deuterated hydrochloric acid, deuterated alcohol saturated with hydrochloride, and deuterated trifluoroacetic acid.

Considering the hydrogen exchange of ferrocene and its derivatives to be one of the simplest instances of electrophilic substitution reactions, it proved of interest to estimate its kinetics in order to have a quantitative characteristic of the relative electrophilicity of the above compounds, and, in particular, to compare it with that of corresponding benzene derivatives. To this end we have studied the hydrogen exchange kinetics of ferrocene, acetyl ferrocene, and benzene in deuterated trifluoroacetic acid. At a molar ratio ferrocene (acetyl ferrocene) : CF_3COOD : benzene = 1 : 3 : 20 (at 25°, $H_o \sim -0.5$) the hydrogen exchange rate constants of ferrocene and acetyl ferrocene were found to amount to $1.62 \cdot 10^{-4} sec^{-1}$ and $1.93 \cdot 10^{-6} sec^{-1}$, respectively, * i.e. the rate of ferrocene was eighty times that of acetyl ferrocene. Under these conditions benzene was not found to be affected and the rate of toluene proved to be three orders lower than that of ferrocene.

It is believed that the investigation of hydrogen exchange of ferrocene and its derivatives in media with different degrees of acidity should result in a quantitative characteristic of the relative electrophilicity of various metallocene and aromatic systems. Such an investigation is in progress and will be reported on later.

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* The deuterium exchange rate constant of acetyl ferrocene was calculated in terms of the exchange data for all hydrogen atoms of the molecule, including the hydrogens of the methyl group.

Tetrahedron Letters No. 2, pp. 43-47, 1961. Pergamon Press, Inc. Printed in the United States of America.

CHLORODIFLUOROMETHANE AS A DIFLUOROMETHYLATING AGENT

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(Received 3 January 1961)

In the study of biologically active compounds the potency-enhancing effects of halomethyl groups have often been observed. Since the electrophilic nature of halomethylenes is clearly indicated by their solvolytic and olefin-addition reactions,[1-8] it was of interest to study the alkylation reactions of dihalo-

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[1] J. Hine, J. Am. Chem. Soc. 72, 2438 (1950) and subsequent papers.

[2] W. E. Doering and A. K. Hoffmann, ibid. 76, 6162 (1954); W. E. Doering and W. A. Henderson, ibid. 80, 5274 (1958).

[3] P. S. Skell and A. Y. Garner, ibid. 78, 5430 (1956).

[4] J. Hine and K. Tanabe, ibid. 80, 3002 (1958) and references therein.

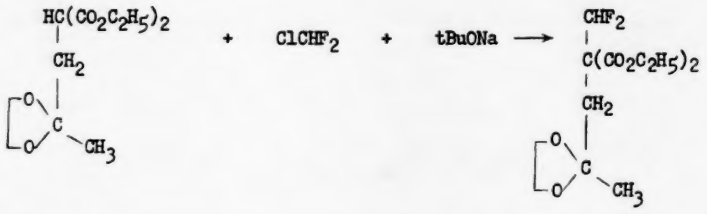
[5] J. Hine and J. J. Porter, ibid. 82, 6118 (1960); J. Hine, R. J. Rosscup and D. C. Duffey, ibid. 82, 6120 (1960).

[6] L. Z. Soborovskii and N. F. Baina, Zhur. Obschei Khim. 29, 1142 (1959); Chem. Abs. 54, 1263 (1960).

[7] J. M. Birchall, G. W. Cross and R. N. Haszeldine, Proc. Chem. Soc. 81 (1960).

[8] Also see reactions with triphenylphosphine, A. J. Speziale, G. J. Marco and K. W. Ratts, J. Am. Chem. Soc. 82, 1260 (1960); S. O. Grim and T. O. Read, ibid. 82, 1511 (1960).

methylene with various nucleophiles as a convenient method of introducing halomethyl groups. Difluoromethylene was first chosen as a model reagent both for the stability of the difluoromethyl group formed in the products and for the ready availability of its precursor chlorodifluoromethane ("Freon 22").[9] Some examples are itemized below. When the sodio derivative of a monoalkylmalonic ester in dimethoxyethane was treated with excess of chlorodifluoromethane, in the presence of sodium t-butoxide, the difluoromethylated derivative (b.p. 105-106° at 0.2 mm , $n_D^{23.5}$ 1.4325) was obtained in 60% yield after fractional distillation. The structure of the difluorinated product was estab-



lished by elementary analyses ($C_{13}H_{20}O_6F_2$ Found: C, 50.65; H, 6.67; F, 11.58) and its characteristic NMR spectrum.[10] As chlorodifluoromethane was shown to be unreactive in the S_N2 type of reaction under the conditions employed,[4] the observed catalytic effect of excess sodium t-butoxide provided further support to the premise that difluoromethylene was involved as an active intermediate in this reaction.

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9 Supplied by the Matheson Co., Inc., East Rutherford, N. J.

10 We are indebted to Dr. N. R. Trenner and Mr. B. Arison of Merck Sharp & Dohme Research Laboratories for interpretations of the NMR spectra.

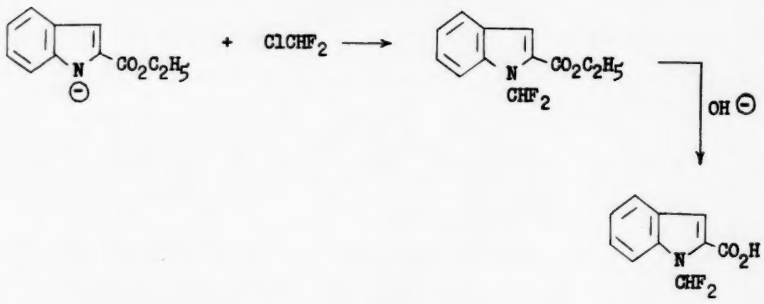
In a similar manner diethyl phenylmalonate was difluoromethylated to the expected ester (b.p. 110° at 0.22 mm , n_D^{23} 1.4741) in 80% yield ($C_{14}H_{16}O_4F_2$ Found: C, 60.03; H, 5.82; F, 10.18).

$$PhCH(CO_2C_2H_5)_2 + ClCHF_2 + tBuONa \longrightarrow Ph\text{-}C(CHF_2)(CO_2C_2H_5)_2$$

Likewise, the anion of diphenylacetonitrile was difluoromethylated at 0° to give α-difluoromethyl-diphenylacetonitrile (m.p. 85°) in excellent yield ($C_{15}H_{11}NF_2$ Found: C, 74.44; H, 4.41; F, 5.89). Hydrolysis of the nitrile afforded α-difluoromethyl-diphenylacetic acid, m.p. 174-6° ($C_{15}H_{12}O_2F_2$ Found: C, 69.15; H, 5.06; F, 14.03).

$$Ph_2\overset{\ominus}{C}\text{-}CN + ClCHF_2 \longrightarrow Ph_2C(CHF_2)(CN) \longrightarrow Ph_2C(CHF_2)(CO_2H)$$

In addition to the facile reactions of difluoromethylene with carbanions, treatment of the sodio derivative of 2-carbethoxyindole with chlorodifluoromethane at 0° readily gave N-difluoromethyl-2-carbethoxyindole (m.p. 95°), instead of a C-alkylated derivative, in very good yield ($C_{12}H_{11}NO_2F_2$ Found: C, 60.58; H, 4.51; F, 13.41). The structure assignment was based on its I.R. (no NH) and NMR spectra. The stability of the N-difluoromethyl group was demonstrated by the saponification of the ester to the corresponding acid (m.p. 184-6° dec.) with 1 N sodium hydroxide ($C_{10}H_7NO_2F_2$ Found: C, 57.09; H, 3.47; F, 16.77). The introduction of a highly electronegative difluoromethyl group at the N-atom apparently exerted a strong hypsochromic and a slight



hypochromic effect on the ultra-violet absorption of the parent 2-carbethoxy-indole chromophore. The infrared spectrum of N-difluoromethyl-2-carbethoxy-indole also indicated considerable interaction of the difluoromethyl group with the neighboring carbonyl group.

The alkylation of 2-hydroxypyridine and related compounds such as carbostyril has been rationalized in terms of the ambident ion theory.[11] When the sodio derivative of carbostyril was treated with difluoromethylene, a mixture of 2-difluoromethoxyquinoline (m.p. 34°, $C_{10}H_7NOF_2$ Found: C, 62.66; H, 3.77; F, 15.58), N-difluoromethyl-α-quinolone (m.p. 98°, $C_{10}H_7NOF_2$ Found: C, 61.94; H, 3.42; F, 17.06; N, 6.92) and two crystalline compounds of m.p. 145-8° ($C_{19}H_{13}N_2O_2F$ Found: C, 71.37; H, 4.03; N, 8.08) and m.p. 210-16° ($C_{28}H_{19}N_3O_3$ Found: C, 75.40; H, 4.19; N, 9.39) was obtained. The extent of O-alkylation observed was evidently indicative of the high electrophilicity

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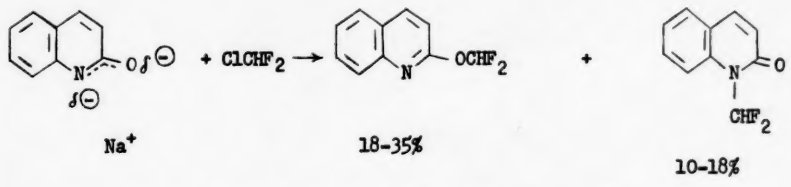
[11] N. Kornblum, R. A. Smiley, R. K. Blackwood and D. C. Iffland, J. Am. Chem. Soc. 77, 6269 (1955) and references therein.



18-35%

10-18%

+ di- and tri-substituted methanes.

of the active species involved in the difluoromethylations. The isolation of the higher melting di- and possibly tri-substituted methanes was reminiscent of the formation of ortho esters and their thio-analogs in the solvolytic reactions of halomethylenes.[4,5] The yields of O- and N-difluoromethylated derivatives of carbostyril were substantially increased at the expense of higher melting byproducts when a proton donor like t-butanol was added. In accordance with the solvolytic mechanism postulated by Hine and co-workers, it may be rationalized that the intermediate ions $>N-\overset{\ominus}{C}F_2$ and $-O-\overset{\ominus}{C}F_2$ were also involved in this case.

Further exploration of this versatile reagent is being continued.

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1961

STRUCTURES OF CYCLOOLEFIN COMPLEXES OF TRANSITION METALS

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(Received 10 January 1961)

IN a continuation of the spectral study of cyclopentadiene complexes of transition metals,[1] we have determined the proton magnetic resonance spectrum (at 56.4 Mc/sec) of the product from reaction of cyclopentadiene and nickel carbonyl.[2] The spectrum indicates unequivocally that this compound is π-cyclopentadienyl π-cyclopentenyl nickel (I) rather than bis(cyclopentadiene)nickel, the isomeric structure originally proposed. The spectrum contains peaks whose position and relative intensities confirm the assignment to five equivalent π-cyclopentadienyl protons (τ = 4.79),[3] three "olefinic" protons (τ = 4.95, 6.12) and four aliphatic protons (τ = 8.92). The cyclopentenyl ring presumably contains and is bound to the metal by a delocalized "π-allylic" system similar to that suggested for allylcobalt and manganese carbonyls.[4]

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[1] M.L.H. Green, L. Pratt and G. Wilkinson, J. Chem. Soc. 3753 (1959); 989 (1960).

[2] E.O. Fischer and H. Werner, Chem. Ber. 92, 1423 (1959).

[3] Location of the resonance lines is in terms of $\tau = 10.000 - (H_{Me_4Si} - H_{sample})(H_{Me_4Si})^{-1}$ where H_{Me_4Si} is the field of resonance of tetramethylsilane inserted as an internal standard.

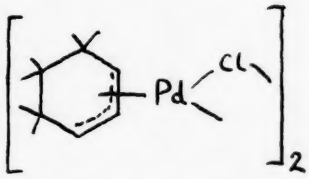
[4] W.R. McClellan, H.H. Hoehn, H.N. Cripps, E.L. Muetterties and B.W. Howk, J. Amer. Chem. Soc. In Press, and references given therein.

I

II

Similarly the palladium complex previously designated as 1,3-cyclohexadiene cyclopentadiene palladium[5] is found to be cyclohexenyl π-cyclopentadienyl palladium(II). The proton resonance spectrum contains peaks assignable to five equivalent π-cyclopentadienyl protons (τ 4.22), three "π-allylic" protons (τ 5.04, 5.18) and six aliphatic protons (τ 8.56).

The present spectral study also confirms the recent suggestion[6] that the product obtained by reaction of 1,3-cyclohexadiene with palladium carbonyl chloride[5] is bis(π-cyclohexenylpalladium chloride)(III).



III

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[5] E.O. Fischer and H. Werner, Chem. Ber. 93, 2075 (1960).

[6] E.O. Fischer, H.P. Kogler and P. Kuzel, Chem. Ber. 93, 3006 (1960).

Presumably the structure is analogous to that of allylpalladium chloride which has been the subject of a recent nuclear magnetic resonance study.[7] As in allylpalladium chloride, the resonance of a single "olefinic" proton occurs at lowest field (τ 4.49) followed by a peak assignable to two equivalent "olefinic" protons (τ 4.78). The resonance of the six aliphatic protons is noted at highest field (τ 8.20).

Details of this work and the extension to other systems will be presented shortly.

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[7] H.C. Dehm and J.C.W. Chien, J. Amer. Chem. Soc. 82, 4429 (1960).

Tetrahedron Letters No.2, pp. 51-54, 1961. Pergamon Press, Inc. Printed in the United States of America.

TRANSANNULAR PHENOMENA IN CYCLIC DIACETYLENES

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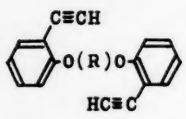
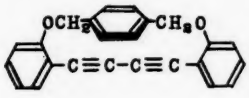
(Received 15 December 1960)

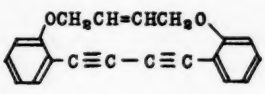
Recently we have shown that the oxidative coupling of α,ω-diacetylenes of type I with cupric acetate in pyridine[1] leads to the cyclic diacetylenes[2]. We have studied the synthesis of the same type of cyclic diacetylenes bearing π-electron system in R to investigate the possibility of transannular interaction with the diacetylenic function.



I



II_p



III_t , III_c

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[1] G. Eglinton and A. R. Galbraith, Chem. & Ind. 1956, 737 ; J. Chem. Soc. 1959, 889.

[2] F. Toda and M. Nakagawa, Chem. & Ind. 1959, 458 ; Bull. Chem. Soc. Japan 33, 223 (1960).

The oxidative coupling of 1,4-bis-(o-ethynylphenoxymethyl)-benzene (I, R= p-xylylene group, m.p. 93～94°C) which was derived from sodium o-ethynylphenoxide and p-xylylene dibromide gave the cyclic monomer, II_p (m.p. 274～275°C, hydrogenated to $C_{24}H_{24}O_2$, m.p. 195～197°C, Mol. wt., 381, calcd., 344). Similarily, the oxidative coupling of the terminal diacetylene (I, R= trans-2-butenylene group, m.p. 118～119°C) which was obtained by the reaction of sodium o-ethynylphenoxide with trans-1,4-dichloro-2-butene yielded the cyclic diacetylene, III_t (m.p. 130°C (decom.), hydrogenated to $C_{20}H_{24}O_2$, m.p. 63.5°C, Mol. wt., 303, calcd., 296). The corresponding o-xylylene isomer, II_o (m.p. 148.5°C (decom.), hydrogenated to $C_{24}H_{24}O_2$, m.p. 180°C, Mol. wt., 346, calcd., 344) and the cis-2-butenylene isomer, III_c

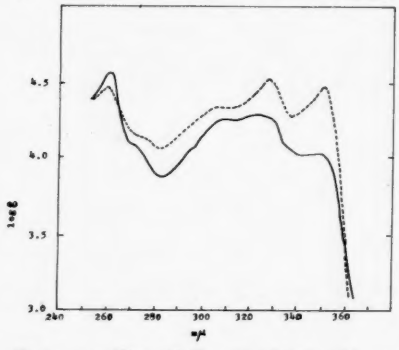

Fig. 1. The U.V. spectra of II_p(——) and IV(-----).

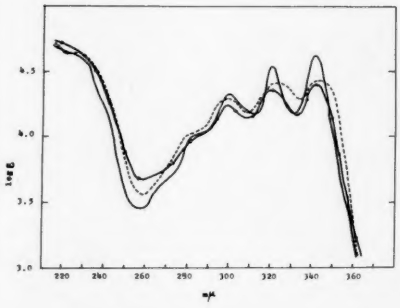

Fig. 2. The U.V. spectra of II_o(—o—o—), III_t(-----) and III_c(——).

(m.p. 154°C (decom.), reduction product was proved to be identical with that of III_t) were prepared according to a similar sequence of reactions.

The ultraviolet spectrum of II_p showed broad and flat absorption peaks as compared with the well defined sharp peaks in the spectrum of o,o'-dibenzyloxydiphenyldiacetylene (IV) as illustrated in Fig. 1. Also the absorption bands arising from the out-of-plane deformation of the adjecent two hydrogen atoms in the p-disubstituted benzene nucleus appeared at 814 cm^{-1} and 796 cm^{-1} in the infrared spectrum of 1,4-bis-(o-ethynylphenoxymethyl)-benzene (I, R= p-xylylene), whereas the corresponding absorption shifted to 776 cm^{-1} in the case of II_p. The same type of an anomalous ultraviolet spectrum was observed in the case of III_t, but could not be seen in the spectra of II_o and III_c (Fig. 2)*.

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* The ultraviolet spectra of III_t, III_c and II_o showed hypsochromic shift of absorption peaks as compared with those of the open chain analogues. This phenomenon could be ascribed to a large ring strain involved in these cycles. Also the presence of a strong absorption minimum at ca. 260 mμ could be attributed to a proximity effect of methylene groups in the bridging chain to the diyne unit. The detailed account of the spectral properties of this series of compounds will be published in near future.

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An examination of the scale models of these diacetylenic cycles reveals that the p-xylylene group in II_p and the trans-ethylenic linkage in III_t are held closely to the diyne unit, on the other hand the o-xylylene group in II_o and the cis-ethylenic linkage in III_c are fixed fairly apart from the diacetylenic bond in the cycles. From these observations, it seems to be highly probable that the anomalousness in the spectra of II_p and III_t is associated with a transannular interaction of π-electrons in the bridging chain with those of the diyne function.

The details of this investigation will be published elsewhere in near future.

Tetrahedron Letters No.2, pp. 55-58, 1961. Pergamon Press, Inc. Printed in the United States of America.

ISOLIERUNG EINES PTERIDINS AUS MYCOBACTERIUM AVIUM

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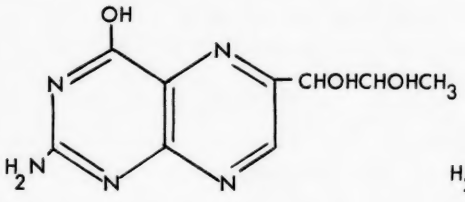
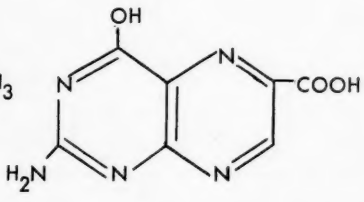
Chemisches Institut der Universität Bonn

(Received 24 December 1960)

AUS 800 g Mycobacterium avium konnten 2 mg eines intensiv blau fluoreszierenden neuen Pteridins I isoliert werden.[1] I zersetzt sich bei 250-280°, ohne zu schmelzen und ist sehr leicht in Alkali und Säure, schwer in Wasser löslich. In Alkohol, Äther, Aceton und Benzol ist die Substanz fast unlöslich. Beim Bestrahlen mit UV-Licht von 360 mμ fluoresziert die Lösung blau, und zwar stark im alkalischen Medium und sehr schwach im sauren Medium. Das Maximum des Fluoreszenzlichtes liegt bei 455 mu (in 0.1-n-Natronlauge).



II



III

[1] F. Korte und H.U. Aldag, Liebigs Ann. 628, 144 (1959).

Tabelle 1. R_F-Werte der Pteridine

	A	B	C
Substanz I	0.04	0.11	0.76
Hydrolysenprodukt IV	0.06	0.20	0.67
Compound C (von Forrest)	0.11	0.30	0.80
Hydrolysenprodukt (Biopterin) II	0.32	0.45	0.66
2-Amino-4-hydroxypteridin (P)	0.38	0.40	0.44
P-6-COOH (2-Amino-4-hydroxy-pteridin-carbonsäure-6) III	0.11	0.14	0.44
P-6-$(CHOH)_3CH_2OH$ (aus Glucose)	0.20	0.28	0.60
P-6-$(CHOH)_3COOH$ (aus Glucuronsäure)	0.09	0.16	0.68

Lösungsmittelsysteme: A = n-Butanol/Eisessig/Wasser (4:1:1), B = 3% wässer. Ammoniumchlorid, C = n-Propanol/1% wasser . Ammoniak (2:1)

Tabelle 2. Elektrophorese der Pteridine

0.05-Mol Lösungen	Essigsäure/ Na-acetat pH 4.65		Ammonium acetat pH 6.8		Natriumhydro-genphosphat pH 8.4
	Anode	Kathode	Anode	Kathode	Anode
P-6-COOH III	106		86		96
P-6-$(CHOH)_3COOH$	86		73		80
Substanz I	64		59		52
2-Amino-4-hydroxy-pteridin		12		0	34
P-6-$(CHOH)_3CH_2OH$		19		6	25
Hydrolysenprodukt IV		16		8	21
Compound C (Forrest)				3	
Biopterin II				13	

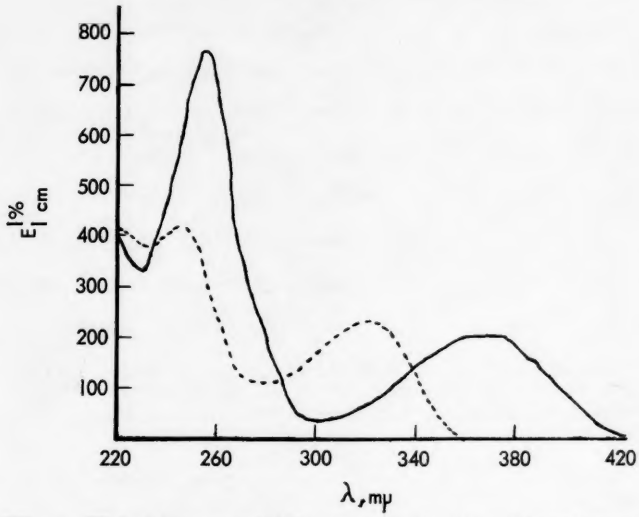


ABB. 1. UV-Spektren von Subst. I: —— in 0.1 n Natronlauge; - - - in 0.1 n Salzsäure.

Die UV-Spektren stimmen im Verlauf der Kurve mit der von Biopterin (II)[2,3] weitgehend überein (Abb.1). Die Substanz I wirkt ebenso als Wuchsstoff wie Biopterin, das für die Entwicklung des Protozoons Chrithidia fasciculata in synthetischer Nährlösung nötig ist. Bei der Behandlung mit Natriumborhydrid oder Natriumamalgam bleibt I unverändert. Durch Kaliumpermanganat wird es zu 2-Amino-4-hydroxypteridin-6-carbonsäure (III) oxydiert. I ist beständig gegen Natronlauge und Licht, während bei Behandlung mit Salzsäure eine neue Substanz (IV) entsteht, die durch

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[2] E.L. Patterson, H.P. Broquist, A.M. Albrecht, M.H. von Saltza und E.L.R. Stokstad, J. Amer. Chem. Soc. 77, 3167 (1955).

[3] H.S. Forrest und H.K. Mitchell, J. Amer. Chem. Soc. 77, 4865 (1955)

Natriummetaperjodat zu III oxydiert wird und das gleiche UV-Spektrum wie Biopterin besitzt; I und IV zeigen ähn-liche R_F-Werte, aber ein verschiedenes Verhalten bei der Elektrophorese. I sowie IV sind weder mit Biopterin noch mit der Compound C [4] von Forrest identisch. I kommt auch bei M. smegmatis und M. phlei vor. Tabelle 1 zeigt die R_F-Werte der Pteridine in verschiedenen Lösungsmittelsystemen und Tabelle 2 die Wanderung der Pteridine zur Anode (mm) nach einer Elektrophorese von 8 Stdn. bei einer Spannung von 8 V/cm.

Wir danken den Herren Dr. H. Seeliger und Dr. U. Bohne für die Züchtung der Bakterien, Herrn Prof.Dr. A. Wacker, Frankfurt für den Chrithidia-Test und Herrn Dr. H.S. Forrest für die Uberlassung einer Probe von Compound C.

Der Alexander von Humboldt-Stiftung dankt Mikiyasu Goto für das Stipendium.

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[4] H.S. Forrest, C. van Baalen und J. Myers, Arch. Biochem. Biophys. 78, 95 (1958).

Tetrahedron Letters No.2, pp. 59-67, 1961. Pergamon Press, Inc.
Printed in the United States of America.

961

STRUCTURE OF GRAYANOTOXIN-I AND -III*

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Nagoya, Japan

(Received 11 January 1961)

GRAYANOTOXIN-I (Andromedotoxin, Acetylandromedol) of Leucothoe grayana is one of the most widely-spread toxic substance in the plants of Ericaceae[1]. It has been shown by Takei et al.[2] that Grayanotoxin-I (G-I) has the molecular formula of $C_{22}H_{36}O_7$, and that alkaline hydrolysis gives acetic acid and Grayanotoxin-III (G-III), $C_{20}H_{34}O_6$, which is also a constituent of the Ericaceae plants[3]. We propose structure I (R=Ac) for G-I and I (R=H) for G-III, respectively, on the following evidence.

The refluxing of G-I, $C_{22}H_{36}O_7$, m.p. 272°, IR: 3540, 1738, 1380, 1250 cm^{-1} with anhydrous copper sulfate in

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* Presented at the 4th symposium on the natural organic products, Kyoto, Japan, October, 1960.

1 T.Takemoto and H.Meguri, Japanese J. Pharm. Chem. 29, 588 (1957).

2 S.Takei and S.Miyazima, J. Agri. Chem. Japan 10, 1093 (1934).

3 H.Kakisawa and M.Kurono, Meeting of Chem. Soc. Japan, Kyoto, Japan, April, 1958.

acetone gave isopropylidene-G-I (II), $C_{25}H_{36}O_5$, m.p. 215°, IR: 3500, 1738, 1650, 1620 cm^{-1}, with loss of two moles of water[4]. Catalytic hydrogenation (2 mol. H_2) of this compound gave the saturated tetrahydro-isopropylidene-G-I (III), $C_{25}H_{40}O_5$, m.p. 163°, IR: 3500, 1736 cm^{-1}, which on chromic trioxide oxidation in pyridine yielded monoketo-tetrahydro-isopropylidene-G-I (IV), $C_{25}H_{38}O_5$, m.p. 186°, IR: 1750, 1740 cm^{-1}. The infrared spectra of IV suggested the presence of a five-membered ring ketone and the absence of hydroxyl group. Since the two double bonds of II are formed by dehydration of the two hydroxyl groups of G-I, it follows that G-I contains no ether linkage and that of the seven oxygen atoms contained in G-I ($C_{22}H_{36}O_7$) five of them should be hydroxyl groups, the remaining two being that of the acetoxyl group.

Three hydroxyl groups in G-III are evidenced to be tertiary because tribenzoyl-G-III (V)[5], $C_{41}H_{46}O_9$, m.p. 170°, is resistant to oxidation with chromic acid.

Both G-I and G-III consumed 1 mole of lead tetra-acetate or sodium metaperiodate to give G-I-ketoaldehyde (VI), $C_{22}H_{34}O_7$, m.p. 216°, IR: 3500, 1736 cm^{-1}, and G-III-ketoaldehyde (VII), $C_{20}H_{32}O_6$, m.p. 249°, IR: 3360, 1730 cm^{-1}, respectively. On the contrary the tribenzoate V and mono-

[4] H.B.Wood, V.L. Stromberg, J.C.Kesesztesy and E.C.Horning, J. Am. Chem. Soc. 76 5689 (1954).

[5] H.Meguri and T.Takemoto, J. Pharm. Soc. Japan 78, 112 (1958).

acetyl-G-I[4] (VIII), $C_{24}H_{38}O_8$, m.p. 244°, were both stable to these reagents. Treating these keto-aldehydes, VI and VII, with alkali readily gave rise to the same unsaturated monoketone (IX), $C_{20}H_{30}O_5$, m.p. 248°, IR: 3430, 1720 cm^{-1}, which has been considered to be an internal aldol condensation product and free from an aldehydic function. From these transformations it is apparent that G-I (and G-III) has a cyclic α-glycol group, one hydroxyl group being tertiary and the other the secondary.

The presence of a secondary acetoxyl group which located in a five-membered ring was shown by oxidation of monoketo-isopropylidene-G-III (X), $C_{23}H_{36}O_4$, m.p. 198°, IR: 3440, 1735 cm^{-1}, obtained by alkaline hydrolysis of IV, to a diketone (XI), $C_{23}H_{34}O_4$, m.p. 200°. The IR spectrum of XI exhibited a single carbonyl peak at 1743 cm^{-1}. This conclusion was further supported by the following evidence. The Wolff-Kishner reduction product of the monoketone IV, a monoalcohol $C_{23}H_{38}O_3$, m.p. 132°, was oxidized to give a monoketone (XII), $C_{23}H_{36}O_3$, m.p. 129°, whose IR spectrum showed an absorption maximum at 1740 cm^{-1} due to a five-membered ring ketone.

Acetylation of isopropylidene-G-I (II) gave monoacetyl-isopropylidene-G-I (XIII), $C_{27}H_{38}O_6$, m.p. 138°, with following NMR[6] peaks: terminal methylene protons (2) at 62 cps.,

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[6] NMR spectra were measured with a Varian Associates instrument (40 Mc.) using 99.5 % deuteriochloroform as solvent and benzene as an external reference.

ethylenic proton (1) at 45 cps., methylprotons attached to ethylenic bond (3) at 181 cps., methylprotons of isopropylidene group (6) at 192 cps., methylprotons of acetoxyl (6) at 170 cps. and methylprotons (6) at 205 cps.

It has been shown cleary that terminal methylene and $H-C=C-CH_3$ system are present in XIII, since ozonisation of keto-isopropylidene-G-I (XIV), $C_{25}H_{34}O_5$, m.p. 184°, IR: 1732, 1745 cm^{-1}, which was obtained by the oxidation of II, produced an appreciable amount of formaldehyde and nortriketo acid, $C_{24}H_{32}O_9$, m.p. 298°, IR: 3500-3000, 1755, 1705 cm^{-1}.

From these data, especially the results of NMR, there should be four methyl groups in G-III; however, the Kuhn-Roth C-methyl determination indicated only three such groups to be present. This difference coupled with a doublet at ca. 1370 cm^{-1} in the IR spectra of all derivatives of G-I suggest the presence of a gem-dimethyl group.

Fig. 1 shows the functional groups of G-I thus obtained.

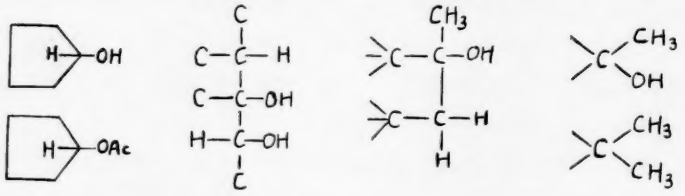


Fig. 1

Oxidation of G-I-ketoaldehyde VI with bromine followed by alkaline hydrolysis gave an α,β-unsaturated acid (XV), $C_{20}H_{30}O_6$, m.p. 215°, methyl ester (XVI), $C_{21}H_{32}O_6$, m.p. 177°.

Ultraviolet absorption of XV at 256 mμ (ε10960) indicated the existence of an α,β-unsaturated ketonic function, which was further shown to be a s-cis-α,β-unsaturated five-membered ring ketone moiety because the 1600 cm^{-1} IR peak intensity was almost comparable to that of the 1705 cm^{-1} carbonyl peak[7].

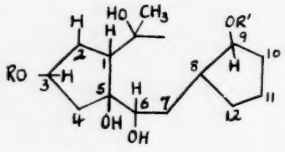
Acid treatment of acid XV or methyl ester XVI readily gave a lactone (XVII), $C_{20}H_{28}O_5$, m.p. 225°, λ_{max}^{EtOH} 253 mμ (ε11200), IR: 3500, 1782, 1705, 1600 cm^{-1}, therefore; a hydroxyl group should be in a γ-position to the carboxyl group in XV. The lactone XV was oxidized with chromic acid anhydride in acetic acid to gave a yellow lactone (XVIII), $C_{20}H_{26}O_6$, m.p. 236°, λ_{max}^{EtOH} 235 (10600), 320 mμ (ε20), IR: 3480, 1780, 1745, 1705 cm^{-1}, which was reduced and discolored by Zn-AcOH. The chemical and spectral characteristics of XVIII were quite similar to cyclopentene-3,5-dione (XIX)[8]. Furthermore, since the infrared and ultraviolet absorptions characteristic of the s-cis-α,β-unsaturated ketone moiety disappeared in XVII, it is apparent that double bond in XV migrates to form an ene-dione system in XVI.

The foregoing results lead to the partial structure XX for G-I (R or R'=Ac) and reactions are summarized in Fig. 2 on the structure XX.

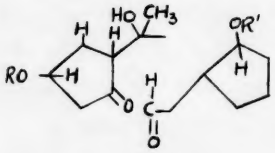
---

[7] E.S.Waight and R.L.Erskine, Steric Effects in Conjugated Systems, p. 73, Butterworths publications Ltd., 1958.

[8] C.H.DePuy and E.F.Zaweski, J. Am. Chem. Soc. 81, 4920 (1959).



XX



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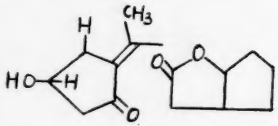
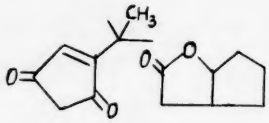
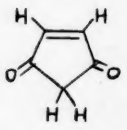


XVII



XVIII

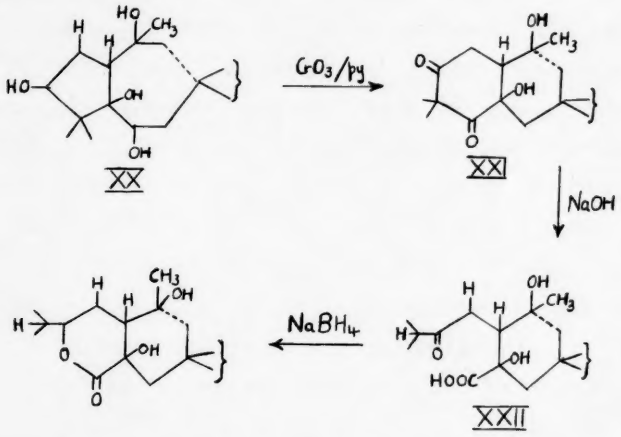


XIX

Fig. 2

Further evidence for XX, and confirmation of the position of the acetoxyl group was acquired through the following reaction: oxidation of G-I with chromic trioxide in pyridine yielded diketo-G-I, (XXI) $C_{22}H_{32}O_7$, m.p. 248°, IR: 3500, 1735, 1713 cm^{-1}; alkaline hydrolysis of this gave the monoketo-acid (XXII), $C_{20}H_{32}O_7$, m.p. 213°, IR: 3450,

1708 cm^{-1}, methyl ester (XXIII), $C_{21}H_{34}O_7$, m.p. 198°. This acid XXII yielded a δ-lactone, $C_{20}H_{32}O_6$, IR: 3480, 1730 cm^{-1}, upon reduction with $NaBH_4$, and a diketo-acid, $C_{20}H_{30}O_7$, m.p. 248°, IR: 3460, 1742, 1700 cm^{-1}, upon oxidation with chromic trioxide in acetic acid, respectively. These transformations are interpreted as follows: the C_9-hydroxyl group in the partial structure XX of G-I is originally acetylated and the remaining two secondary hydroxyl groups are oxidized with simultaneous acyloin migration[9] to a β-diketone XXI and these transformed as indicated below.



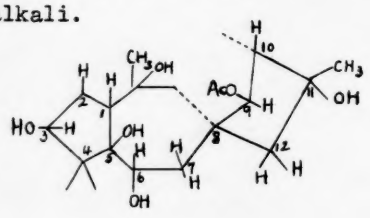
Hydrolysis of monoketo-isopropylidene-G-I (XIV), followed by oxidation with chromic trioxide in pyridine afforded

9 D.G.Hardy, W.Rigby and D.P.Moody, J. Chem. Soc. 2955 (1957). W. Cocker, J.T.Edward, T.F.Holley and D.M.S. Wheeler, Chem. Ind. 1485 (1955).

diketo-isopropylidene-G-III (XXIV), $C_{23}H_{30}O_4$, m.p. 213°, IR: 1740, 1748, 1660, 1625 cm^{-1}. Its NMR spectra, besides peaks assigned due to terminal methylene (30 cps.), H-C=C-CH_3 (50 cps. and 178 cps.), isopropylidene-dimethyl (197 cps.) and gem-dimethyl (207 cps.), showed a quartet at 80 cps. arising from the C_6-hydrogen in partial structure XX; thus C_7 should have two hydrogen atoms.

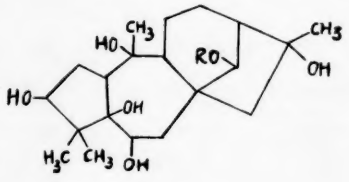
Evidence has been obtained which suggests a H-C=C-CH_3 system occupying a position β to C_9 in partial structure XX. Namely, monoketo-isopropylidene-G-I (XIV) was oxidized by OsO_4 and alkaline hydrolysis gave a mixture of pentol and triol. Further oxidation of this mixture with sodium metaperiodate yielded triketo-aldehyde, $C_{22}H_{30}O_7$, m.p. 234°, the mother liquor of which furnished another compound, α,β-unsaturated keto-aldehyde, $C_{23}H_{26}O_5$, m.p. 235°, λ_{max}^{EtOH} 232 mμ (ε13300), IR: 2880, 1760, 1715, 1670 cm^{-1}, when chromatographed on alumina.

From these results it is possible to extend the partial structure XX for G-I to XXV. C_{10}-hydrogen in XXV must be in a bridge-head position because the diketone XXIV was not converted to an α,β-unsaturated ketone when treated with alkali.



XXV

Selenium dehydrogenation of G-III yielded a very small amount of aromatic hydrocarbon which was characterized as trinitrobenzene adduct m.p. 141°, λ_{max}^{EtOH} 252, 260, 330, 340, 346, 366, 390 mμ; since the ultraviolet spectrum is very similar to that of anthracene, it is quite reasonable to ascribe an alkyl anthracene structure for the dehydrogenation product. Since G-I is a tetracyclic and since two rings are present as five-membered rings, the formation of an alkylanthracene from G-III should require a rearrangement during the course of dehydrogenation and also the presence of a seven-membered ring adjacent to one of the five-membered rings. These facts coupled together with biogenetic considerations lead to structure I (R=Ac) and I (R=H) for Grayanotoxin-I and -III, respectively.



I

Several data not given in this communication also support these structures.

The authors wish to express their thanks to Dr. Y. Yukawa, Osaka University, for NMR measurments.

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MASS SPECTROMETRIC EVIDENCE FOR THE STRUCTURE OF IBOXYGAINE AND ITS TOSYLATE

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Department of Chemistry, Massachusetts Institute of Technology, Cambridge, Mass.

(Received 13 January 1961)

THE structure of iboxygaine[1] and its carbomethoxy derivative voacangarin[2] (= voacristin[3]) has been investigated recently in three laboratories[1,2,3] and expressions Ia [2] and Ib [1,3] have been proposed for the former. One of the remarkable reactions of iboxygaine is the facile quaternization of its tosylate which cannot be isolated in its covalent form. This quaternary salt occupies a central position in the structural arguments for iboxygaine since its conversion[2] into ibogaine[4] (IIIa) is the only correlation with a compound of known structure. For this tosylate both structures IIa [1,2] and IIb [3] have been suggested.

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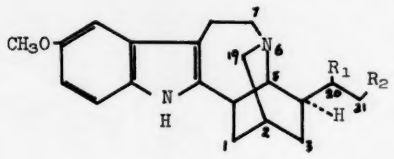
[1] R. Goutarel, F. Percheron and M. M. Janot, Compt. rend. 246, 279 (1958).

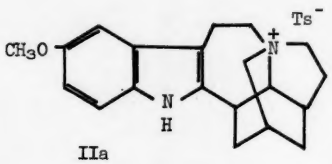
[2] D. Stauffacher and E. Seebeck, Helv. chim. Acta 41, 169 (1958).

[3] U. Renner and D. A. Prins, Experientia 15, 456 (1959).

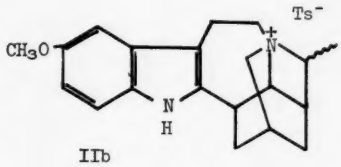
[4] M. F. Bartlett, D. F. Dickel and W. I. Taylor, J. Am. Chem. Soc. 80, 126 (1958). For stereochemistry see G. Arai, J. Coppola and G. A. Jeffrey, Acta. Cryst. 13, 553 (1960).



Ia R_1=H, R_2=OH
Ib R_1=OH, R_2=H
IIIa R_1=R_2=H
IIIb R_1=D, R_2=H



IIa



IIb

We have now obtained conclusive evidence for structures Ib and IIb for iboxygaine and its tosylate, respectively, by their conversion into specifically monodeuterated ibogaine and locating the position of the deuterium atom in this molecule by mass spectrometry: On reduction of iboxygaine tosylate[2] (42 mg , m.p. 267-8° [3]) with lithium aluminum deuteride in tetrahydrofuran, **ibogaine** was obtained in quite pure[5] form (m.p. 146-9°; 82% yield). One recrystallization from ethanol/water raised the m.p. to 150-51°, undepressed on admixture of authentic IIIa.

The mass spectrum[6] of this product corresponded to the one[7] of IIIa

---

[5] The mass spectrum of this crude material did not indicate any appreciable by-products.

[6] The spectra were determined with a CEC 21-103C mass spectrometer equipped with a heated inlet system operated at 140°; electron energy 70 eV.

[7] K. Biemann, Tetrahedron Letters 15, 9 (1960). The sample of ibogaine used in the present investigation had been recrystallized repeatedly to remove a small amount of ibogamine, the presence of which contributed to the peaks mass 279 and 280 in the spectrum published previously.

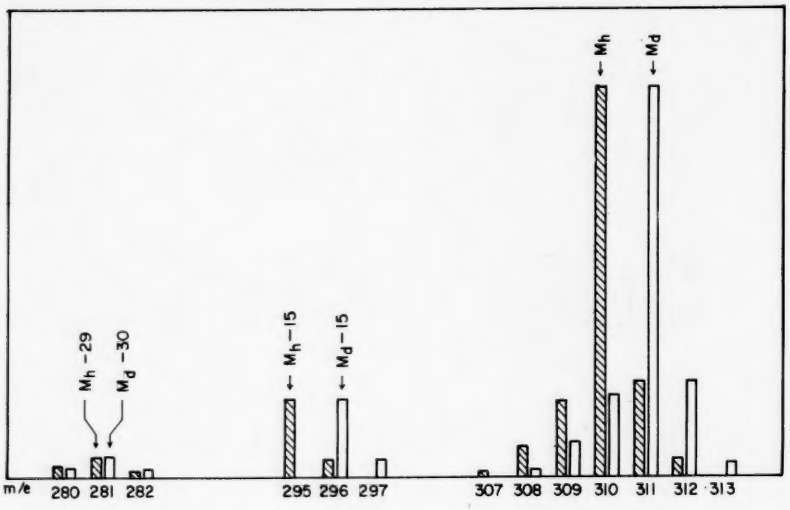


Figure 1

except that certain peaks were displaced for +1 mass unit. In Fig. 1 the spectrum of the deuterated sample (light peaks) is compared with ibogaine (shaded peaks) in the region of m/e 280-313. The presence of one atom of deuterium in the former is evidenced by its molecular weight (designated M_d) of 311 vs. 310 (designated M_h) for IIIa. The methyl group is lost in both cases as 15 mass units, and the deuterium atom is, therefore, not located in this group, thus excluding structure Ia. (The methyl group of the methoxyl cannot be responsible for the peaks at m/e 295 and 296, respectively, since also ibogamine, lacking the methoxyl, exhibits[7] the corresponding peak at m/e 265.) The deuterium atom is, however, present in the ethyl group because both spectra exhibit a peak at m/e 281; i.e. this fragment is formed by the loss of 29 mass units (C_2H_5) from ibogaine and of 30 mass units (C_2H_4D) from the deuterated compound, which is, therefore, IIIb. In the rest of the spectrum the isoquinuclidine peaks appear at m/e 123,

124, 125, 136, 137, 149, 150, 151 and are thus shifted for one mass number, whereas the indole peaks remained at 186 and 225 as in IIIa. This pattern is in agreement with a deuterium atom at C_{20}[8] on the basis of a more detailed interpretation of the spectrum which will be presented in the full paper.

These results demonstrate that in the deuteride reduction of the tosylate a bond between N_6 and C_{20} was opened, and the structure of the cation must thus be IIb. Iboxygaine is, therefore, Ib and not Ia. The other isomeric structures (OH at C_5,C_7 or C_{19}) which conceivably could also lead to IIb are excluded for the following reasons: (a) The only saturated product isolated after treatment of the tosylate with sodium hydroxide[3] is iboxygaine itself; i.e. the bond formed in the quaternization was reopened in this displacement reaction, and there is no reason to assume that the deuteride should exclusively displace another bond. (b) The acid-stability of iboxygaine - one mode of formation from voacangarin requires prolonged heating with hydrochloric acid[2] - precludes the presence of an azetidine ring in iboxygaine, and (c) the tosylate of Ib is the only one of all four possible isomers which would be expected to quaternize so easily. The four-membered ring in IIb, the supposed strain of which led some of the earlier investigators[1,2] to discard structure IIb as impossible, is in fact part of an azapinane system and thus not unduly strained.

Acknowledgments - The authors are indebted to Dr. D. Stauffacher, Basel, for samples of iboxygaine and voacangarin and to the National Science Foundation for financial support (Grant G5051).

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[8] Numbering system according to ref. 4.

Tetrahedron Letters No.2, pp.72-75, 1961. Pergamon Press, Inc. Printed in the United States of America.

THE SYNTHESIS OF CONESSINE FROM THE CORRESPONDING 3-KETO-Δ^4-UNSATURATED SYSTEM

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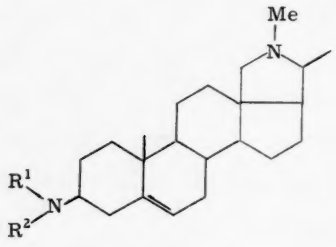
Department of Chemistry, University of Wisconsin, Madison, Wisconsin

and Department of Chemistry, Stanford University, Stanford, California

(Received 12 January 1961)

IN connection with studies directed toward the total synthesis of conessine, I ($R^1 = R^2 = Me$), we have been in search of a facile method for its production from a 3-oxygenated derivative. The results of previous studies[1] toward this objective were not promising, e.g. reaction of dimethylamine with a 3β-p-toluenesulfonate-Δ^5-unsaturated steroid gave, at best, very poor yields of the desired product.



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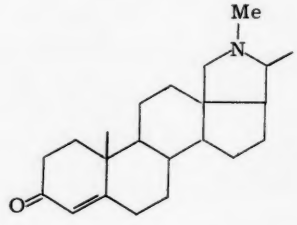

II

[1] E. J. Corey and W. R. Hertler, J. Am. Chem. Soc. 81, 5209 (1959).

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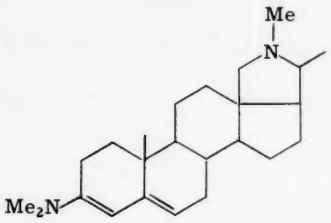

III

The selective reduction of an enamine like III to yield I (R^1 = R^2 = Me) was considered an attractive possibility, because the former substance promised to be readily accessible[2] from Δ^4-conanene-3-one (II).[3] In the present work a new direct approach to the latter ketone was developed. Conessine was converted, by the action of cyanogen bromide, into cyano-iso-conessimine, I (R^1 = Me, R^2 = CN), which, on alkaline hydrolysis, was transformed into iso-conessimine, I (R^1 = Me, R^2 = H), as previously described.[4] This product, on treatment with N-chlorosuccinimide or t-butyl hypochlorite (to produce I, R^1 = Me, R^2 = Cl) followed by dehydrohalogenation with sodium ethoxide, then hydrolysis,[5] afforded in 62% yield

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[2] Cf. F. W. Heyl and M. E. Herr, J. Am. Chem. Soc. 75, 1918 (1953).

[3] R. Pappo, U. S. Patent No. 2,913,455, Nov. 17, 1959; Chem. Abst. 54, 3527 (1960). In our hands the method of A. Bertho and M. Goetz, Ann. 619, 96 (1958) failed.

[4] S. Siddiqui and R. H. Siddiqui, J. Indian Chem. Soc. 11, 787 (1934).

[5] Cf. W. E. Bachmann, M. P. Cava and A. S. Dreiding, J. Am. Chem. Soc. 76, 5554 (1954).

Δ^4-conanene-3-one (II), m.p. after purification 108.5-110°, $\lambda_{max}^{95\%\ EtOH}$ 241 mμ (ε 16,000) (Found: C, 80.5%; H, 10.2%; N, 4.3%). Mixed m.p. determinations and infrared spectroscopy demonstrated the identity of this material with that of Pappo.[3]

1961

Treatment of II with anhydrous dimethylamine in the presence of magnesium sulfate and a trace of p-toluenesulfonic acid in a sealed tube (exclusion of air) readily gave the enamine III, m.p. 151-152°, (after recrystallization from acetone) $\lambda_{max}^{Et_2O}$ 271 mμ (ε 18,400) (Found: C, 81.0%; H, 10.8%; N, 8.0%). Despite the known resistance of such enamine systems to reduction by lithium aluminum hydride[6] we tried the reaction of III with sodium borohydride and, to our pleasure, found that reduction occurred smoothly and selectively to give conessine, I ($R^1 = R^2 = Me$), as the major and only isolable product.

Prior to the experiments described above we carried out a study with Δ^4-cholestene-3-one which, under the conditions already mentioned, was converted readily into 3-dimethylamino-3,5-cholestadiene, m.p. 97-99°, λ_{max}^{ether} 272 mμ (ε 19,000) (Found: C, 84.1%; H, 11.8%; N, 3.9%). Reduction with sodium borohydride afforded 3β-dimethylamino-Δ^5-cholestene, m.p. 151-151.5° (reported,[7] 151°). The new synthetic

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[6] G. B. Spero, J. L. Thompson, B. J. Magerlein, A. R. Hanze, H. C. Murray, O. K. Sebek, J. A. Hogg, J. Am. Chem. Soc. 78, 6213 (1956).

[7] D. P. Dodgson and R. D. Haworth, J. Chem. Soc. 67 (1952).

sequence for converting a Δ^4-3-keto-steroid into the 3β-dialkylamino-Δ^5-unsaturated derivative thus promises to be generally applicable.

Acknowledgement. We are most grateful to Dr. Raphael Pappo of G. D. Searle Co. for a gift of conessine and for supplying us with a specimen of Δ^4-conanene-3-one for comparison purposes. We also wish to thank the U. S. Public Health Service and the National Science Foundation for grants which have supported this work in part.

Tetrahedron Letters No.2, pp. 76-81,1961. Pergamon Press, Inc. Printed in the United States of America.

STEROID TOTAL SYNTHESIS--BENZHYDRINDANE APPROACH

PRELIMINARY SURVEY

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College of Engineering and Technology, Calcutta
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Indian Institute of Science, Bangalore

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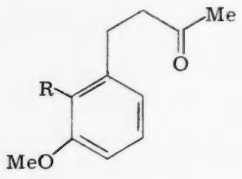
(Received 16 January 1961)

IN view of the recent report of Barnes and Miller[1] on a synthesis of desoxyequilenin, we are prompted to disclose some of the results of a long-range Indian-American collaborative study on steroid synthesis that involves a similar basic approach.



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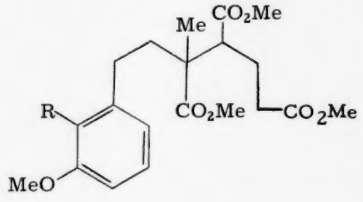
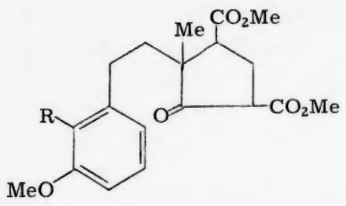
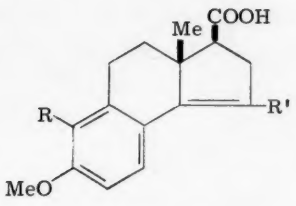


II

[1] R. A. Barnes and R. Miller, J. Am. Chem. Soc. 82, 4960 (1960).



III



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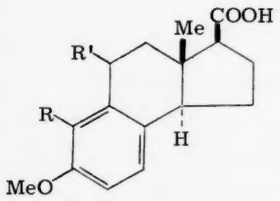

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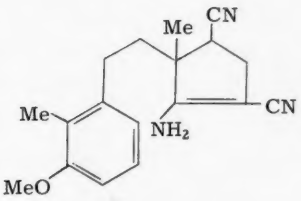

VI

m-Methoxybenzylacetone, I (R = H), was converted into the triester II (R = H) in 63% yield by the following reaction sequence: condensation with ethyl cyanoacetate, addition of hydrogen cyanide, cyanoethylation, hydrolysis, and esterification. Dieckmann cyclization gave the keto diester III (R = H) which on acid-catalyzed ring closure, followed by hydrolysis and decarboxylation, afforded the acid IV (R = R' = H), m.p. 227-228°. Catalytic hydrogenation of this acid proceeded stereoselectively to give (see below) the trans-benzhydrindane derivative V (R = R' = H).

A similar study was carried out with the ketone I (R = Me), which was best obtained, among other ways, by the Stobbe condensation of the isobutyl enol ether of 2-methyldihydroresorcinol[2] with di-t-butylsuccinate,

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[2] A. Eschenmoser, J. Schreiber and S. A. Julia, Helv. Chim. Acta 36, 482 (1953).

followed by heating with palladium-on-carbon to effect removal of the carbo-t-butoxyl group, and aromatization. The resulting 3-methoxy-2-methyl-β-phenylpropionic acid, m.p. 170.5-172.5°, was converted via the acid chloride, into the methyl ketone I (R = Me), b.p. 112-114° (0.1 mm); 2,4-dinitrophenylhydrazone, m.p. 126-128°.

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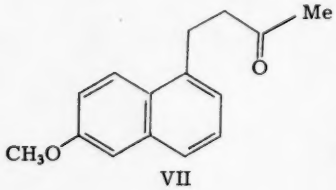
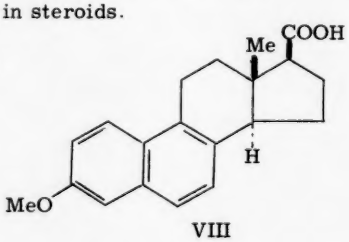
The ketone I (R = Me) was converted, by a sequence similar to that outlined above for the nor series, into the acid IV (R = Me, R' = H), m.p. 267.5-269 (methyl ester, m.p. 136-137°), thence to the reduced substance V (R = Me, R' = H), m.p. 248.5-249° (methyl ester, m.p. 115-116°).

The best method for preparing V (R = Me, R' = H) involved condensation of I (R = Me) with t-butyl cyanoacetate (product, m.p. 78-78.5°), addition of hydrogen cyanide (product, m.p. 81.5-82°), and cyanoethylation to give a mixture of diastereomers, m.p. 145-146°. Pyrolysis at 175° removed the carbo-t-butoxyl group to give the trinitrile corresponding to II (R = Me) which on t-butoxide-catalyzed Thorpe cyclization yielded two isomeric forms of VI, m.p. 167-168° and 148.5-149°. The mixture of isomers was submitted to acid hydrolysis followed by cyclization with hydrogen fluoride (two isomers, m.p. 242.5-243.5° and 183-184°), then, without separation of isomers, alkaline hydrolysis to yield IV (R = Me, R' = COOH), m.p. 247-250°. Decarboxylation and hydrogenation yielded V (R = Me, R' = H) in 41% over-all yield from the ketone I (R = Me).

A similar study with I (R = H, and CN β to the keto group) has led to the stereoselective production of the diacid V (R = H, R' = COOH), m.p. 212-213°(dec.), having an additional carboxyl group located at the position (R') corresponding to C_{11} in steroids.

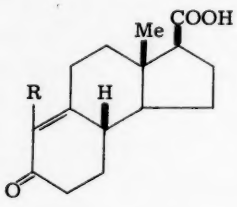


VII

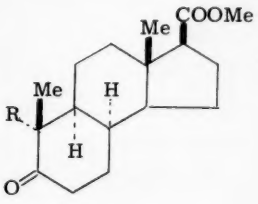


VIII

Evidence for the stereochemical course of the reduction of the substances IV (R' = H, R = H or CH_3) was provided by studying a related series where the configurations were ascertainable. β-(6-Methoxy-1-naphthyl)ethyl bromide[3] on treatment with potassium cyanide in acetone, followed by saponification, yielded β-(6-methoxy-1-naphthyl)propionic acid, m. p. 160-161°, which was converted via the acid chloride (dimethyl cadmium) into the methyl ketone VII, m. p. 48. 5-50°. Condensation of VII with ethyl cyanoacetate, followed by addition of hydrogen cyanide, cyanoethylation (adduct, m. p. 118. 5-120°), hydrolysis and treatment with diazomethane gave a triester, m. p. 94-95. 6°. Dieckmann reaction followed by cyclization with hydrogen fluoride gave the tetracyclic diester, m. p. 174-174. 8°, which was saponified (diacid, m. p. 260-262°), decarboxylated (mono acid, m. p. 260-262. 5°), and hydrogenated to give a single product, m. p. 283. 5-285. 5° (dec.). That this substance was the acid VIII with a trans C/D juncture was proved by establishing its identity with authentic material prepared from dl-equilenin methyl ether[4] via the cyanohydrin which was dehydrated, hydrogenated and finally hydrolyzed.



IX



X

[3] W. E. Bachmann, W. Cole and A. L. Wilds, J. Am. Chem. Soc. 61, 974 (1939); 62, 824 (1940).

[4] W. S. Johnson, J. W. Petersen, C. D. Gutsche, J. Am. Chem. Soc. 69, 2942 (1947).

Birch reduction of V (R = Me) gave IX (R = Me). The identity of this substance with material prepared in connection with the Woodward steroid synthesis[5] provided conclusive proof of the configuration in our series and established an obvious pathway to completion of the steroid synthesis utilizing the Woodward method of attaching ring A. The yield of IX (R = Me), however, was extremely poor in contrast with that of the lower homolog; the Birch reduction of V (R = H) proceeded readily to give IX (R = H), m. p. 246-248° (vac.). Moreover cyanoethylation of the system IX (R = Me) is known[5] to yield a mixture of epimers at C_{10} (steroid numbering). Therefore we chose to explore a route which promised to be more stereoselective.

Demethylation of V (R = Me, R' = H) afforded the phenolic acid, m. p. 245.5-249° (vac.) which, on hydrogenation in aqueous alkaline solution over ruthenium oxide was converted, in high yield, into a single alcohol, m. p. 203-203.5°. This substance was esterified with diazomethane and oxidized with Sarett reagent to afford the keto ester X (R = H), m. p. 82-82.5°. Cyanoethylation afforded X (R = CH_2CH_2CN), m. p. 142.5-143°, as the exclusive product, which on hydrolysis was converted into the corresponding keto diacid, m. p. 208-211°. The dimethyl ester X (R = $CH_2CH_2CO_2Me$) melted at 80.5-81.5°. Epimerization at C_8 (steroid numbering) would yield a known substance which has been converted to a natural steroid. So far attempts to effect this epimerization have failed. (The bromo diester, m. p. 161-162.5°, could not be converted into the desired 6,7-dehydro X (R = CH_2CH_2COOMe) by the usual methods.) This problem is currently under investigation; also studies on the alkylation of the methyl ester of IX (R = H) are in progress.[6]

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[5] R. B. Woodward, F. Sondheimer, D. Taub, K. Heusler and W. M. McLamore, J. Am. Chem. Soc. 74, 4223 (1952).

[6] Satisfactory analytical and spectral properties have been obtained for the new substances reported herein.

Acknowledgement: We are indebted to the following agencies for support of this work: The National Institutes of Health, the National Science Foundation, the Wisconsin Alumni Research Foundation, the Allied Chemical and Dye Corporation, and the Sterling-Winthrop Research Institute.

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STRUCTURES OF PARTHENIN AND AMBROSIN[1]

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The Florida State University
Tallahassee, Florida

(Received 30 January 1961)

Degradation and consideration of n.m.r. spectra dictate revision of the structure of parthenin[3] and ambrosin[3-6] to I and II, the dehydrogenation results previously[3,6] reported being the results of a typical carbonium ion rearrangement.

The n.m.r. spectra (see table) of I, II and anhydroparthenin (III) contain two low-field doublets (intensity one proton each) associated with the cyclopentenone system, each doublet of II being split again due to spin coupling with hydrogen at C_1. A second pair of doublets, each representing one proton, is characteristic of the C_{11}-methylene group conjugated with the lactone function, as may be

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1. Supported in part by grants from the National Science Foundation (NSF-G 14396) and the U.S. Public Health Service (RG-5814).

2. Recipient of a Fulbright Travel Award, 1959-1960.

3. W. Herz and H. Watanabe, J. Am. Chem. Soc. 81, 6088 (1959).

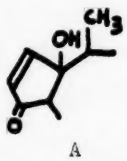
4. H. Abu-Shady and T. D. Soine, J. Am. Pharm. Assoc. 42, 387 (1953); 43, 365 (1954).

5. L. Bernardi and G. Büchi, Experientia 13, 466 (1957).

6. F. Šorm, M. Suchý and V. Herout, Coll. Czechoslov. Chem. Commun. 24, 1548 (1959).

seen in the n.m.r. spectrum of coronopilin[7] (IV), a substance isolated from related plants[7]. Thus, I, II and III contain four vinyl protons.

In converting I to III, the sharp methyl singlet of I moves to higher, not lower, field and the methyl doublet disappears, being replaced by a sharp band characteristic of $=\overset{|}{\underset{R}{C}}-CH_3$. These observations, and the information given earlier[3], can be accommodated by the partial structure A, as can the deoxygenation of I with zinc-acetic acid which results in V (one vinyl triplet, two sharp doublets - intensity one hydrogen each - due to the relatively unshielded hydrogen of C_3). An analogous compound is formed by dehydration of dihydroisoparthenin (VI).



A

II also has one unsplit and one split methyl signal, both at high field. The methyl singlet is found in all derivatives of I and II which we have studied and points to the presence of a tertiary methyl group.

The lactone ring is closed to C_8 (isolation of artemazulene) which carries a hydrogen atom and is adjacent to a fully substituted carbon atom (sharp doublet near 300 c.p.s. in the n.m.r. spectra of I, II, III, IV, and the tetrahydroderivatives VII and VIII, singlet at lower field in VI and

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7. W. Herz and G. Högenauer, unpublished experiments

dihydroambrosin (IX). Since parthenin is not an α-ketol[3], the tertiary methyl group is located at C_5.

Formation of acetic acid and optically pure S-(+)-α-methylglutaric acid (m.p. 80-82°, $(\alpha)_D^{24}$ 20° [8]) in 25% yield by permanganate oxidation of norparthenone whose spectroscopic properties and reactions are in full accord with the postulated structure demonstrates the nature of the C_1-C_{10}-C_9-C_8-C_7 fragment and establishes the absolute configuration at C_{10} (methyl β). Dehydration experiments suggest that the neighboring hydroxyl group is α, but this cannot be regarded as proved. Comparison of the rotatory dispersion curves of I, II and their hydrogenation products with those of model steroids[9] indicates only moderate correspondence of amplitudes which, because of the lack of the C_1 sesquiterpene epimers prevents us from making definite assignments at this time.

The n.m.r. spectra of helenalin, balduilin and isotenulin are similar to those reported here in that they indicate the presence of four vinyl protons (two in the case of isotenulin) and one tertiary methyl group. Hence revision of currently accepted formulae is in order[10].

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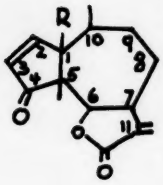
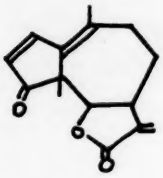
8. A.Fredga, Svensk Kem. Tidskr. 67, 343 (1955); Arkiv. Kemi, Mineral Geol. 24A, No. 32 (1947).

9. F. Sondheimer, S. Burstein and R. Mechoulam, J. Am. Chem. Soc. 82, 3209 (1960). This paper also presents ultraviolet data which support the above formulae.

10. Forthcoming publication. We suggest structures analogous to those of I and II, with the lactone ring closed to C_8.



I R=OH
II R=H



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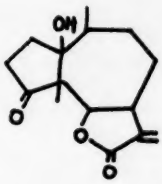
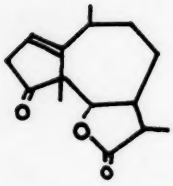
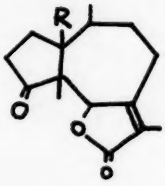


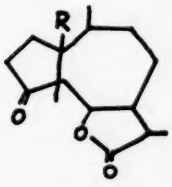
IV



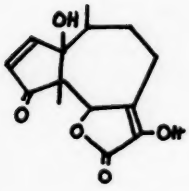
V



VI R=OH
IX R=H



VII R=OH
VIII R=H



X

Whether the biogenesis of these compounds involves the irregular union of one isoprene and one C_{10} - unit or whether they arise by methyl migration from C_4 to C_5 prior or subsequent to cyclization cannot be stated at present.

N.M.R. Spectra (60 mc. in $CDCl_3$, internal standard tetramethylsilane)[11]

I. 63, 71(C_{10}-methyl), 77(C_5-methyl), 301, 308(H_6), 335 and 338, 376 and 379 (methylene), 368, 373 (H_3), 450, 456 c.p.s. (H_2).

II. 61, 67(C_{10}-methyl), 71(C_5-methyl), 276, 285 (H_6), 329 and 332, 376 and 379 (methylene), 364, 367, 370, 373 (H_3), 446, 448, 452, 454 c.p.s. (H_2).

III. 81(C_5-methyl), 122(C_{10}-methyl), 264, 271 (H_6), 336 and 339, 376 and 378 (methylene), 362, 368 (H_3), 475, 481, c.p.s. (H_2).

IV. 68(C_5-methyl), 70, 77(C_{10}-methyl), 297, 304 (H_6), 336 and 339, 371 and 374 (methylene) c.p.s.

V. 69, 71, 76, 77(C_{10}-and C_{11}-methyl), 78(C_5-methyl), 173, 175.5, 181.5, 183.5. (2 protons, H_3), 251, 259 (H_6) 356.5, 358, 360 c.p.s. (H_2).

VI. 50(C_5-methyl), 61.5, 69(C_{10}-methyl), 108(C_{11}-methyl, 332 br. c.p.s. (H_6).

VII. 65.5, 67, 73(C_{10}-and C_{11}-methyl), 67(C_5-methyl), 279, 284 c.p.s. (H_6).

VIII. 61, 69(C_{10}-methyl), 70(C_5-methyl), 65, 73(C_{11}-methyl), 268, 273.5 c.p.s.(H_6).

IX. 50(C_5-methyl), 57, 63(C_{10}-methyl), 109.5(C_{11}-methyl) 280 br. c.p.s. (H_6).

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[11] Spectra were run by Mr. Fred Boerwinkle of our Department and Mr. L. F. Johnson of Varian Associates. We are grateful to Mr. Johnson and to Dr. M. T. Emerson for assistance with the assignments.

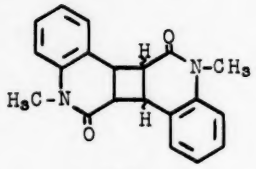
Tetrahedron Letters No.2, p.87, 1961. Pergamon Press, Inc. Printed in the United States of America.

1961

ERRATUM

EDWARD C. TAYLOR and W.W. PAUDLER: Photodimerization of some α,β-unsaturated lactams, Tetrahedron Letters No. 25, 1-3 (1960).

The authors apologise for the omission of the N-methyl groups in formulas III and IIIa on p. 3 of the above article. The correct structures are given below:



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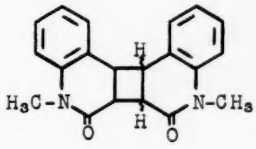

IIIa

Tetrahedron Letters No. 3, pp. 89-91, 1961. Pergamon Press Ltd. Printed in the United States of America.

ADDITION REACTION OF NITRILE OXIDES ON CYCLOOLEFINS

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(Received 13 February 1961)

IN pursuing our studies on the addition reaction of nitrile oxides on olefins[1] to give Δ^2-isoxazolines:

we have examined the reactions of semicyclic and endocyclic ethylenic double bonds, in order to establish some rules which could be useful in differentiating several orders of reactivity. Analogous study has been made for instance by Alder and Stein[2] on the addition reaction of phenylazide and olefins.

It was already known that some cycloethylenic derivatives, such as benzo- and naphtho-quinone,[3] bicyclopentadiene,[4] 3,6-endomethylene-1,2,3,6-

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[1] A. Quilico, G. Stagno d'Alcontres and P. Grünanger, Nature, Lond.166, 226 (1950); A. Quilico and coworkers, Gazz. Chim. Ital. 80 140, 479, 741, 831 (1950) and following papers; The ethylenic derivatives tested up to now are over 200.

[2] Alder and Stein Liebigs Ann. 485, 211 (1931); 515, 165, 185 (1935).

[3] A. Quilico and G. Stagno d'Alcontres, Gazz. Chim. Ital. 80, 140 (1950).

[4] A. Quilico, P. Grünanger and R. Mazzini, Gazz.Chim.Ital.82,349 (1952).

tetrahydrophthalic anhydride,[5] indene[6] and fulvenes,[4] are reactive towards benzonitrile oxide, while some other double bonds taking part in aromatic systems, such as benzene, furan, thiophene, pyrrole, indole, etc. do not react, at least under normal experimental conditions.

We have now tested with positive results the compounds listed in Table 1, and have obtained in every case the corresponding Δ^2-isoxazoline.

TABLE 1

Ethylenic compound	No.	Adduct with benzonitrile oxide m.p. or b.p./mm	Yield %
Cyclopentene	I	38.5-39.5°; 145°/1 mm	85
1-Methylcyclopentene	II	54-56°	41
1-Phenylcyclopentene	III	99-100°	55
Cyclopentadiene	IV	(mol.1:1) 47-48°; 137°/0.5	48
Cyclopentadiene	V	(mol.1:2) 182.5-184°	40
Cyclopent-1-en-3-one	VI	95-96°	almost quant
Cyclopent-1-en-3, 5-dione	VII	202° dec.	61
Cyclohex-1-en-3-one	VIII	oxime m.p. 167-168°	22
3,5-Dibromocyclopent-1-ene	IX	109°	56
Acenaphthylene	X	201°	96
Methylenecyclopentane	XI	79.5-80°	almost quant
Methylenecyclohexane	XII	84-84.5°	80
Methylenecycloheptane	XIII	65-67°	69,5
β-Pinene	XIV	97.5-98.5°	91
3,6-Endoxo-1,2,3,6-tetrahydro-phthalic anhydride	XV	215°	90

[5] A. Quilico and P. Grünanger, Gazz.Chim.Ital. 82, 140 (1952).

[6] G. Stagno d'Alcontres and P. Grünanger, Gazz.Chim.Ital. 80, 831(1950); G.W. Perold and F.V.K. v.Reiche, J.S.Afr.Chem.Inst. 10, 5 (1957).

All the products have been obtained by reaction at ordinary temperature or slightly above, and, except for compound VIII, with good to quantitative yields. Cyclopentadiene reacts, as expected, with 1 or 2 moles of benzonitrile oxide. The adduct with cyclohexenone was formed in low yield (22%). The structure of the Δ^2-isoxazolines has been demonstrated, when necessary, on the base of the $LiAlH_4$ reduction products[7].

On the contrary, the following compounds do not react with benzonitrile oxide, at least under usual conditions (reaction in ethereal solution at room temperature or on slight boiling):

cyclohexene
1-methylcyclohexene
1-phenylcyclohexene
phenanthrene

From the foregoing results, experimental details of which will be published elsewhere, we might deduce the following conclusions:

(a) ethylenic double bonds present in a five-membered ring react easily with nitrile oxides, whereas double bonds present in six-membered rings do not react, unless they are activated by conjungation, i.e. with a carbonyl group.

(b) whereas endocyclic double bonds are reactive only in cyclopentene series, semicyclic double bonds of methylenecycloalkanes are always reactive, giving spirocompounds.

Considering the ready preparation of the reagent, the easiness of execution of the test and the fact that Δ^2-isoxazolines are usually well crystallizable solids, the addition reaction with nitrile oxides represents a useful discriminating tool for the identification of cycloethylenic double bonds.

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[7] G.W. Perold and F.V.K. v.Reiche, J.Amer.Chem.Soc.79,465 (1957).

Tetrahedron Letters No. 3, pp.92-94, 1961. Pergamon Press Ltd. Printed in the United States of America.

SYNTHESIS OF 1-METHYLENEPYRROLIZIDINE

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Institute of Pharmacology and Chemotherapy

Academy of Medical Sciences, U.S.S.R.

(Received 13 February 1961)

LATELY a considerable increase has been observed in the number of pyrrolizidine alkaloids not containing necinic acid. A new addition is 1-methylenepyrrolizidine recently isolated by Culvenor and Smith from Crotolaria anagyroides.[1]

In line with our programme for the synthesis of pyrrolizidine alkaloids[2-4] we have carried out the synthesis of natural 1-methylene-pyrrolizidine. Condensation of ethyl prolinate with methyl acrylate (boiling time, 24 hours) yielded ethyl β-(N-2-ethoxycarbonylpyrrolidine) propionate (1), 74%, b.p.$_{1\ mm}$ 92-94°, n_D^{20} 1.4571 (Found: C, 57.78; H,8.40, N, 6.08. Calc. for $C_{11}H_{19}O_4N$: C, 57.58: H, 8.39; N, 6.11). Picrate, m.p. 74.5 - 75.5° (EtOH) (Found: N, 12.14. Calc. for $C_{17}H_{22}O_{11}N_4$: N, 12.22). I was heated with dry C_2H_5ONa in xylene (150-160°, 1.5 hours)

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[1] C.C. Culvenor and L.W. Smith, Austr. J. Chem. 12, 255 (1959).

[2] N.K. Kochetkov, A. M. Likhosherstov and E.I. Budovskii, Khim. Nauka i Prom. 4, 678 (1959); Zh. Obshch. Khim. 30, 2077 (1960).

[3] N.K. Kochetkov, A.M. Likhosherstov and L.M. Likhosherstov, Zh. VKhO.im. Mendeleeva 5, 109 (1960).

[4] N.K. Kochetkov and A.M. Likhosherstov, Zh. VKhO. im. Mendeleeva, 5, 477 (1960).

and the crude ketoester on heating with 10% HCl (boiling time, 3 hours) was converted to pyrrolizidone-1 (II)[5]; yield 65%, b.p.$_{3\ mm}$ 55-56°, n_D^{20} 1.4884 (Found: N, 11.49. Calc. for $C_7H_{11}ON$: N, 11.19). Picrate m.p. 162-164° (abs. EtOH, decomp.) (Found: C, 44.04; H, 4.12. Calc. for $C_{13}H_{14}O_8N$: C,44.06; H, 3.98).

In order to pass over to methylenepyrrolizidine use was made of Wittig's reaction. As far as we know this is the first time it has been applied in the field of alkaloids. By reaction with excess freshly-prepared triphenylphosphinomethylene[6] in ether (boiling time, 6 hours, standing at room temperature for 2 days) II was transformed to racemic 1-methylene-pyrrolizidine (III). Yield 63%, colorless, hygroscopic liquid, b.p.$_{168\ mm}$ 114-116°, n_D^{20} 1.4880 (Found: C,77.95; H, 10.60; N, 11.15. Calc. for $C_8H_{13}N$: C, 77.99; H,10.64; N, 11.37). Picrate m.p. 213-213.5° (EtOH. Found: C,47.50; H,4.57. Calc. for $C_{14}H_{16}O_7N_4$: C, 47.73; H, 4.58). The I.R. spectrum of III completely coincided with that of the natural product.[1] It contains an intensive 884 cm^{-1} methylene band and does not contain the 1385 cm^{-1} band characteristic of isoheliotridene-1,2 derivatives, thus proving the absence of isomerization during the Wittig reaction.

Racemic III was resolved by conversion to the tartrate with d-tartaric acid and after crystallization from ethanol-ethyl acetate (1:2) mixture the

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[5] This compound has also been used by us in the synthesis of isoretronecanol.[4] It was simultaneously prepared by Adams, employing another method [R. Adams, S. Miyano and D. Flis, J. Amer. Chem. Soc. 82, 1466 (1960)].

[6] G. Wittig, H. Eggers and P. Duffner, Liebigs Ann. 619, 10 (1958).

less soluble tartrate of m.p. 103-104° was isolated, $[\alpha]_D^{21}$+8°(c 3.52, 96% EtOH) (Found: C, 52.90; H,6.93. Calc. for $C_{12}H_{19}O_6N$ C, 52.72; H,7.01). The 1-methylenepyrrolizidine base was liberated from the tartrate by the action of K_2CO_3 or NH_3 in aqueous solution. It was found to completely coincide with the natural alkaloid, $[\alpha]$ -39° (Found: C,77.99; H,10.58; N, 11.37). Picrolonate m.p. 171.5-172° (EtOH. Found: C,55.79; H,5.43; N, 17.80. Calc. for $C_{18}H_{21}O_5N_5$: C,55.81; H,5.46; N,18.07) Picrate m.p. 214-215° (Found: C, 47.58; H, 4.55; N, 15.85. Calc. for $C_{14}H_{16}O_7N_4$: C, 47.74; H, 4.58; N, 15.91) (Reported data:[1] $[\alpha]_D^{20}$-43.1° (c 1.07, EtOH). Picrolonate m.p. 171-172.5°. Picrate m.p. 217.5-218°.

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1961

RÉACTIONS PHOTOCHIMIQUES DU DIPHÉNYL-1,4 CYCLOHEPTADIÈNE-1,3

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(Received 13 February 1961)

L'IRRADIATION des systèmes cycliques à doubles liaisons conjuguees en lumière ultra-violette ou visible peut donner lieu, selon les conditions opératoires et la structure des systèmes envisagés, à des transformations variées : photooxydation,[1] photoisomérisation,[2,3,4] photodimérisation.[5] Nous rapportons ici l'exemple d'un composé diénique conjugué qui peut subir l'une ou l'autre des deux premières réactions photochimiques : il s'agit du diphényl-1,4 cycloheptadiène-1,3 III.

Par condensation, à la température ordinaire, du phényl-lithium (2.6 moles) sur la cycloheptanedione-1,4 I[6] (1 mole), nous avons obtenu, avec un rendement de 60 %, l'un seulement des deux diphényl-1,4 cycloheptanediols-1,4 stéréoisomères,II. F = 110-111° (Trouvé : C, 81.0 ; H,7.9.

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[1] Ch. Dufraisse, Experientia Supplementum II p.27. Birkhäuser Verlag, Basel (1955).

[2] D.H.R. Barton, Helv. Chim. Acta. 42,2604 (1959)

[3] W.G. Dauben et G.J. Fonken, J. Amer. Chem. Soc. 81, 4060 (1959).

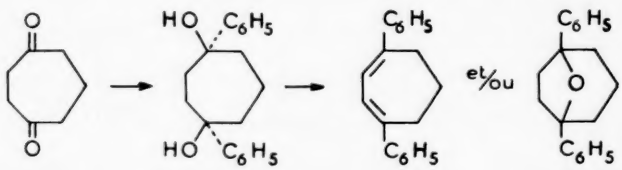
[4] O.L. Chapman et D.J. Pasto, J. Amer. Chem. Soc. 82, 3642 (1960).

[5] A. Mustafa, Chem. Rev. 51, 1 (1952).

[6] J. Rigaudy et P. Courtot, C.R. Acad.Sci., Paris 248, 3016 (1959).

Calculé pour $C_{19}H_{22}O_2$: C, 80.81 ; H, 7.85%). Le spectre I.R. de ce dialcool laissait prévoir une structure cis (OH libre à 3590 cm^{-1} - OH lié intramoléculaire à 3470 cm^{-1} en sol. diluée CCl_4), ce qui a été ultérieurement confirmé par son obtention à partir du photooxyde V par hydrogénation catalytique.

L'action des déshydratants habituels sur ce diol est assez complexe car elle se traduit soit par une monodéshydratation conduisant à l'époxyde IV, soit par une double déshydratation aboutissant au diène III. Les deux réactions sont souvent simultanées ; ainsi le chauffage avec de l'acide oxalique anhydre ou avec du bisulfate de potassium conduit-il à des mélanges de III et IV, qui peuvent être résolus par chromatographie sur alumine.



I II III IV

La monodéshydratation est la plus facile. Par dissolution du diol II dans de l'acide acétique contenant 10 % d'acide sulfurique, ou par un bref chauffage à 135° dans l'acide formique, on obtient essentiellement l'époxy-1,4 diphényl-1, 4 cycloheptane IV, F = 85° (Trouvé : C, 86.25 ; H,7.8 ; H mob.,0. Calculé pour $C_{19}H_{20}O$: C, 86.32 ; H,7.63 ; H mob., 0 %) . I.R. (CCl_4) : 1020 cm^{-1} (vibration C.O.C.).

Le dialcool est déshydraté plus difficilement en diène conjugué : le chauffage au reflux dans l'acide acétique contenant 10 % d'acide sulfurique donne avec un rendement de 40 % le diphényl-1,4 cycloheptadiène-1, 3 III. F = 98°

Forte fluorescence bleue en lumière U.V. (Trouvé : C, 92.45 ; H.7.5. Calculé pour $C_{19}H_{18}$: C, 92.63 ; H,7.37 %). Le maximum principal d'absorption dans l'U.V. [λ_m= 316 ; log ϵ = 4.47 (hexane) - λ_m= 318 mμ ; log ϵ = 4.38 (éthanol)] exclut toute structure isomère possédant des doubles liaisons non conjuguées. Le produit fixe 2.15 ± 0.15 moles H_2 par mole en présence de noir de Pd.

La solution du diène III (10^{-2}M) à 16° dans l'éthanol absolu contenant une trace d'éosine, et dans laquelle on fait passer un courant d'oxygène, est irradiée par une lampe "Philips-Episcope" de 500 W. La disparition du diène étant suivie par spectrophotométrie à 316 mμ, on constate que la réaction est terminée après 90 min et on isole aisément après lavage au méthanol le photooxyde V pur avec 90 % de rendement : aiguilles incolores. F = 96-96.5° (Trouvé : C, 82.0 ; H, 6.6. Calculé pour $C_{19}H_{18}O_2$: C, 81.98 ; H, 6.52 %) . L'épidioxy-1,4 diphényl-1,4 cycloheptène-2 V oxyde instantanément l'iodure en iode en présence d'acide acétique ; il fixe rapidement une première mole d'H_2, puis une deuxième plus lentement, en présence de noir de Pd, pour donner quantitativement le dialcool II précédemment décrit, ce qui permet d'attribuer à ce dernier la structure cis.

Cette réaction n'est pas le premier exemple de photooxydation en série cycloheptadiénique, car Cope et al.[7] ont préparé par la même méthode l'épidioxy-1,4 cycloheptène-2. Mais dans ce dernier cas, le phénomène paraissait beaucoup plus lent (144 hr) et le photooxyde isolé avec un rendement relativement faible (29 %) donnait par hydrogénation un peu de diol trans à côté du cis, ce qui laissait suspecter la présence de peroxydes polymères.

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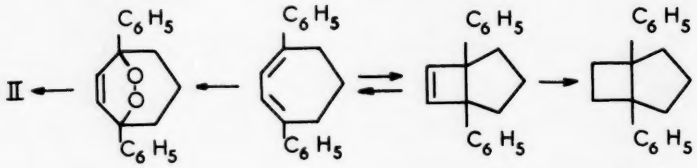
7 A.C. Cope, T.A. Liss et G.W. Wood, J. Amer. Chem. Soc. 79, 6287 (1957).



V III VI VII

Le photoisomère se forme par exposition à la lumière solaire de la solution du diène III (4.10^{-3} M) dans l'éther anhydre. En suivant comme précédemment la diminution de l'absorption diénique par spectrophotométrie à 316 mμ, nous avons constaté que la réaction était terminée après 6 hr d'irradiation par soleil brillant. On recueille ainsi avec un rendement quasi quantitatif le diphényl-1,4 bicyclo [3.2.0] heptène-2 VI. F = 70-71° (Trouvé : C, 92.4; H, 7.45. Calculé pour $C_{19}H_{18}$: C, 92.63 ; H, 7.37 %). Il redonne intégralement le diène III par chauffage sous vide 1 hr à 270° ; la détermination de sa masse moléculaire par cryoscopie dans le benzène (Trouvé 259 ± 26. Calculé : 246.33) exclut la possibilité d'une dimérisation. Le photoisomère VI est hydrogéné catalytiquement en présence de noir de Pd avec absorption de 1.05 ± 0.06 moles H_2 par mole, pour donner le composé saturé VII, le diphényl-1,4 bicyclo [3.2.0] heptane. F = 72.5-73° (Trouvé : C, 91.9 ; H, 8.1. Calculé pour $C_{19}H_{20}$: C, 91.88 ; H, 8.12 %). D'autre part le spectre I.R. (CS_2) de VI présente à 748 cm^{-1} une bande provenant de la vibration gauche des hydrogènes fixés symétriquement en cis sur une double liaison, bande signalée pour d'autres photoisomères cyclobuténiques[3,4] et qu'on ne trouve pas dans le spectre du dérivé dihydrogéné VII. Enfin le spectre de R.M.N.[8] (CCl_4 - Réf. interne : tétraméthylsilane) s'accorde tout à fait avec le haut degré de symétrie

[8] Dû à l'obligeance du Dr. A. Melera de la Société Varian A.G. (Suisse) que nous remercions ici.

de la structure VI. On y note en effet la présence d'une raie très fine (δ = 6.23 p.p.m.) correspondant aux deux H oléfiniques, un signal dû aux six protons (δ = 1.95 p.p.m.) cyclopentaniques et une raie fine (δ = 6.83 p.p.m.) provenant de la résonance des dix protons benzéniques et qui laisse présumer l'absence de double liaison conjuguée avec les noyaux aromatiques.

Nous avons en outre remarqué que cette photoisomérisation aboutit au même résultat, que l'irradiation soit effectuée avec barbotage d'air ou sous vide.

Nous venons d'avoir connaissance de la mise en évidence par Chapman et Pasto[9] d'une photoisomérisation analogue dans le cas du cycloheptadiène-1,3 et de quelques-uns de ses dérivés ; la réaction paraît donc très générale dans cette série.

Il est intéressant de souligner la grande netteté avec laquelle le diphényl-1,4 cycloheptadiène-1,3 donne les deux réactions, photooxydation et photoisomérisation, lorsqu'on le place dans des conditions d'irradiation et de solvant différentes. Nous avons entrepris une étude systématique des divers facteurs pouvant orienter la transformation photochimique dans un sens ou dans l'autre. Les résultats de ce travail seront publiés dans un mémoire ultérieur.

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[9] O.L. Chapman et D.J. Pasto, Chem. & Ind. 53 (1961).

Tetrahedron Letters No.3, pp.100-104, 1961. Pergamon Press Ltd.,
Printed in the United States of America.

TRITERPENOID COMPOUNDS. 7β-HYDROXY-A_1-BARRIGENOL[1]

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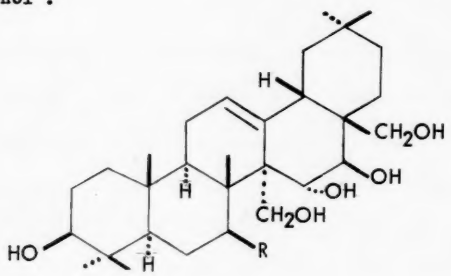
(Received 1 February 1961)

THE hexahydroxy-triterpene compound, $C_{30}H_{50}O_6$, m.p. 308-310°, $[\alpha]_D$ + 37° (dioxan) isolated from Pittosporum undulatum Vent.[2] and P. phillyraeoides DC.[3] is now identified as 7β-hydroxy-A_1-barrigenol or 3β,7β,15α,16β,27,28-hexahydroxyolean-12-ene (I; R = OH) on the basis of the structure (I; R = H) proposed for A_1-barrigenol[2].



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[1] Part IV: H.R. Arthur, A.R.H. Cole, Miss K.J.L. Thieberg and D.E. White, Chem. and Ind. 926 (1956).

[2] A.R.H. Cole, D.T. Downing, J.C. Watkins and D.E. White, Chem. and Ind. 254 (1955).

[3] A.L. Beckwith, A.R.H. Cole, J.C. Watkins and D.E. White, Austral. J. Chem. 9, 428 (1956).

We have not been able to obtain an acetate resembling that described by Cornforth and Earl[4] so that we cannot confirm the previous suggestion[2] that our compound is pittosapogenin[4]. However, by comparison of our compound and its acetate with R_1-barrigenol and its acetate[5] (NMR, IR and mixed m.p.) we have shown that our compound is identical with R_1-barrigenol.

7β-Hydroxy-A_1-barrigenol gives a yellow colour with tetranitromethane, resists hydrogenation over Adams catalyst and shows the characteristic absorption at 1654, 836 and 810 cm^{-1} (Nujol) of a tri-substituted double bond. Biogenetic considerations and preparation of a hexa-acetate, m.p. 186-187.5°, $[\alpha]_D$ - 28°, a tetrabenzoate, m.p. 333.5-334°, $[\alpha]_D$ + 24°, a diethylidene, m.p. 236-237°, $[\alpha]_D$ + 47.5°, and a di-isopropylidene derivative, m.p. 218-219°, $[\alpha]_D$ + 39°, suggested that it might be a hydroxy-A_1-barrigenol. The tetrabenzoate was oxidised to a bright yellow, non-enolisable α-diketone, m.p. 307.5-308.5°, $[\alpha]_D$ + 46°, [ϵ_{max} 40 at 443 mμ and 241 at 333 mμ (dioxan)] and the hexa-acetate to a conjugated ketone, m.p. 233.5-234°, $[\alpha]_D$ - 13.5° [ϵ_{max} 12,960 at 242 mμ; 1752 (acetates) and 1672 cm^{-1}], products strongly reminiscent of A_1-barrigenyl tribenzoate diketone and 11-oxo-A_1-barrigenyl penta-acetate[2].

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[4] J.W. Cornforth and J.C. Earl, J. Proc. Roy. Soc. N.S. Wales 72, 249 (1938).

[5] Yau-Tang Lin, Tung-Bin Lo and Su-Chan Su, J. Chinese Chem. Soc. (Taiwan) Ser. II, 4, 77 (1957).

The diethylidene derivative, characterised as the x, y-diacetate, m.p. 313-313.5°, $[\alpha]_D$ + 35°, formed an x-oxo-y-acetate, m.p. 319-321°, $[\alpha]_D$ + 56°, by selective oxidation and acetylation. The oxo-acetate gave a positive Zimmermann reaction and afforded the x,y-diacetate on reduction with lithium aluminium hydride and reacetylation. These reactions indicate that the x-hydroxyl is 3β.

More vigorous oxidation of the 3β,y-diol formed a 3,y-dioxo compound, m.p. 280-282.5°, $[\alpha]_D$ + 9°. This is stable to potassium permanganate, and hence cannot be an aldehyde.

Partial hydrolysis of the diethylidene-3β,y-diacetate gave the y-hydroxy-3β-acetate, m.p. 304.5-306°, $[\alpha]_D$ + 42°, and a trace of the isomeric 3β-hydroxy-y-acetate, m.p. 282.5-284°, $[\alpha]_D$ + 41° (mixed m.p. 261-286°). The 3-monoacetate was oxidised to the y-oxo-3β-acetate, m.p. 295-299°, $[\alpha]_D$ - 27°, which failed to form a semicarbazone and did not give a Zimmermann test. Lithium aluminium hydride reduction of the y-oxo-3β-acetate or the 3,y-diketone yielded the 3β,epi-y-diol, m.p. 298-300°, $[\alpha]_D$ + 37°. Mild acetylation afforded the epi-y-hydroxy-3β-acetate, m.p. 322.5-323°, $[\alpha]_D$ + 46°, dehydrated by phosphoryl chloride in pyridine to the anhydro-3β-acetate, m.p. 248-248.5°, $[\alpha]_D$ + 104.5°, which has the cis-disubstituted double bond of a cyclo-olefin (absorption at 1682 (in CCl_4) and 752 and 738 cm^{-1} (in CS_2)). Hydrogenation over Adams catalyst in acetic acid formed a diethylidene-3β-acetate, m.p. 284.5-285°, shown by mixed m.p. and infrared comparison to be identical with diethylidene-A_1-barrigenyl acetate (15α, 27:16β, 28-di-O-ethylidene-olean-12-en-3β-yl acetate), m.p. 285-285.5°, $[\alpha]_D$ + 53°.

Hydrolysis of the anhydro-acetate followed by oxidation of the intermediate alcohol, m.p. 217-219°, $[\alpha]_D$ + 103°, yielded the anhydro-3-ketone, m.p. 275-278°, which contained an isolated keto group (band at 1705 cm^{-1}) hence proving that the y-function cannot be in ring A.

Substituents at $C_{(y)}$ absorb at 3613 (hydroxyl), 1747 (acetate), 1737 (ketone) and 3433 cm^{-1} (epi-hydroxyl). We consider these displaced values are due to the close proximity of these groups to one pair of ethylidene oxygen atoms. This could occur if $C_{(y)}$ were $C_{(7)}$ or $C_{(22)}$ but the oxidation of the y-hydroxyl to a hindered ketone which, with lithium aluminium hydride, affords the readily dehydrated epi-y-hydroxyl is at variance with the known behaviour at $C_{(22)}$[6]. Hence the equatorial 7β-position is indicated.

This was confirmed by autoxidation of the diethylidene y-keto-3β-acetate in the presence of potassium t-butoxide[7]. This

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[6] C. Djerassi, E. Farkas, A.J. Lemin, J.C. Collins and F. Walls, J. Amer. Chem. Soc. 76, 2969 (1954); A. Sandoval, A. Manjarrez, P.R. Leeming, G.H. Thomas and C. Djerassi, J. Amer. Chem. Soc. 79, 4468 (1957); G. Cainelli, A. Melera, D. Arigoni and O. Jeger, Helv. Chim. Acta 40, 2390 (1957).

[7] D. Arigoni, D.H.R. Barton, E.J. Corey, O. Jeger et al., Experientia 16, 41 (1960).

afforded a diosphenol identified by its ultraviolet absorption (ϵ_{max} 3000 at 279 mμ changing to 1500 at 328 mμ in alkaline solution) and thus demonstrated the presence of the group $>CH-CH_2-CO-\overset{|}{C}-$. This confirms the suggestion that our hexahydroxy compound is 7β-hydroxy-A_1-barrigenol.

Satisfactory analyses have been obtained for all compounds mentioned, except the diosphenol which was not isolated. Infrared measurements are on carbon tetrachloride solutions and ultraviolet on ethanol solutions unless otherwise indicated.

We are greatly indebted to Dr. A.R.H. Cole and his collaborators for the infrared measurements and their interpretation, to Professor Y-T. Lin for the samples of R_1-barrigenol and its acetate, to Professor M. Shamma and Mr. Ralph Mumma for NMR spectra and to Professor D.H.R. Barton and Mr. John Templeton who carried out the autoxidation.

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POSITION OF THE AROMATIC METHOXYL IN AMARYLLIDACEAE ALKALOIDS RELATED TO POWELLANE

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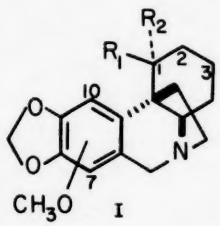
Amaryllidaceae alkaloids related to powellane[1] (I, R_1, R_2 = H) possess a methoxyl group whose position at either C_7 or C_{10} on the aromatic nucleus



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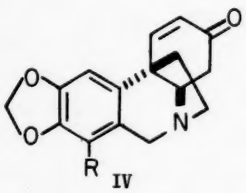

IV

has been a matter for conjecture. On the basis of the difference in ultraviolet extinction coefficient between derivatives with and without substituents at the C_1 position, Warnhoff and Wildman[2] assigned the methoxyl to the 10-position. As they noted, such a formulation readily fits the biogenetic scheme (cf. II ⟶ III, route A) proposed by Barton and Cohen.[3] However, the

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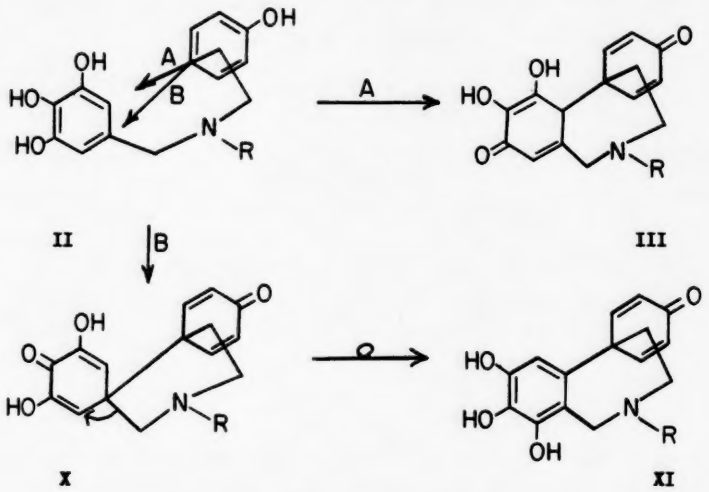
[1] These include powelline, nerbowdine, undulatine, crinamidine and buphanamine; cf. W. C. Wildman, The Alkaloids Vol. VI, p. 289. R. H. F. Manske, ed. Academic Press, Inc., New York, 1960.

[2] E. C. Warnhoff and W. C. Wildman, J. Am. Chem. Soc. 82, 1472 (1960).

[3] D. H. R. Barton and T. Cohen, Festschrift Arthur Stoll ed. by E. Jucker, Birkhauser, Basel, 1957, p. 117.



recent observation that dihydrobuphanamine (I, R_1 = H, R_2 = OH) and epidihydrobuphanamine (I, R_1 = OH, R_2 = H) exhibit hydroxyl stretching frequencies (3599 cm.$^{-1}$ (OH$\longrightarrow\pi$) and 3616 cm.$^{-1}$ (free OH) respectively) nearly identical with their Ar-demethoxy analogues (3602 cm $^{-1}$ (OH$\longrightarrow\pi$) and 3616 cm.$^{-1}$ (free OH) respectively), is not in agreement with this assignment. Molecular models indicate that either configuration of the C_1 hydroxyl should show evidence of hydrogen bonding if the methoxyl is in the 10-position. This evidence supports assignment of the methoxyl to the 7-position.

Comparison of the nuclear magnetic resonance spectra of oxocrinine (IV, R = H)[1] and dihydrooxocrinine (IV, R = H, no double bond at C_1 - C_2) allows the clear differentiation of the absorption from the 7- and 10-protons, for only the latter is appreciably affected by hydrogenation.

Nuclear Magnetic Resonance Data

	Aromatic Protons		Olefinic Protons		Benzylic Protons
	C_7	C_{10}	C_1	C_2	C_6
Oxocrinine	2.66	2.25	1.49	3.09; J=10	4.80, 5.30; J=17
Dihydrooxocrinine	2.68	2.43			4.80, 5.30; J=17
Oxopowelline		2.50	1.53	3.04; J=10	4.90, 5.30; J=17

The spectra were observed at 60 mc., using benzene as an external standard; to convert the data to p.p.m. relative to tetramethylsilane as 10.00 the value of 2.73 p.p.m. was assumed for benzene.[4] The resonance of the sole aromatic proton of oxopowelline (IV, R = OCH_3)[1] is that anticipated for the C_{10} proton, for the shift relative to the proton at C_{10} of oxocrinine corresponds to the observed effect of the aromatic methoxyl (0.23 p.p.m.).[4] The resonance peaks of the olefinic protons of oxopowelline and oxocrinine are essentially the same, although the former would surely be affected by a C_{10} methoxyl. Further, the absorption of one of the benzylic protons of oxopowelline at C_6 shows the effect of the C_7 methoxyl.

Chemical evidence showing conclusively that the methoxyl group is at the 7- position now has been obtained. (+)-Powellane (V)[5] was converted with sodium in liquid ammonia to the phenol VI,[6] m.p. 245-7°, $[\alpha]_{589}^{24}$ 8.6° (c 0.65, methanol) (Found: C, 73.93; H, 8.12; OCH_3, 11.85. $C_{16}H_{21}NO_2$ requires: C, 74.10; H, 8.16; OCH_3, 11.96). This was converted with diazomethane to the

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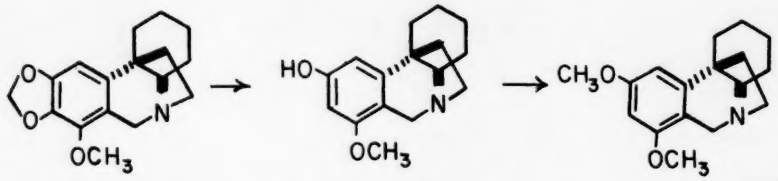
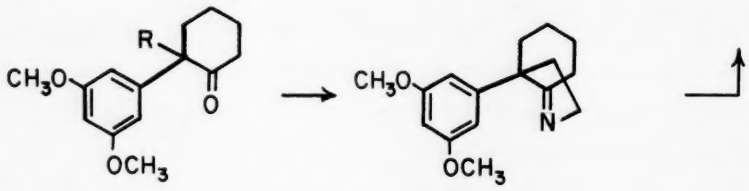
4 L. M. Jackman Application of Nuclear Magnetic Resonance Spectroscopy in Organic Chemistry. Pergamon Press, New York, 1959, p. 63.

5 W. C. Wildman, J. Am. Chem. Soc. 80, 2567 (1958).

6 cf. D. B. Clayson, J. Chem. Soc. 2016, 1949. We are grateful for discussions with Professor A. J. Birch of the University of Manchester concerning the applicability of the method to this problem.



V VI VII



VIII IX

oily ether VII, $[\alpha]_{589}^{24}$ 11.4° (c 0.69, chloroform) (Found: C, 74.25; H, 8.43; OCH_3, 22.95. $C_{17}H_{23}NO_2$ requires: C, 74.69; H, 8.48; 2 OCH_3, 22.71); picrate, m.p. 238-9° (Found: C, 55.09; H, 5.15; N, 11.24. $C_{23}H_{26}O_9N_4$ requires: C, 54.97; H, 5.22; N, 11.15). The ketone VIII (R = H), m.p. 62.5-63° (Found: C, 71.64; H, 8.01; OCH_3, 26.82. $C_{14}H_{18}O_3$ requires: C, 71.77; H, 7.74; OCH_3, 26.49) was converted to an oily keto ester VIII (R = $CH_2CH_2COOCH_3$) with methyl acrylate (Found: C, 67.61; H, 7.71. $C_{18}H_{24}O_5$ requires: C, 67.48; H, 7.55). This was subjected to a Curtius degradation giving the imine IX, isolated as the picrate, m.p. 164-8° (Found: C, 54.04; H, 4.97; N, 11.46. $C_{22}H_{24}N_4O_9$ requires: C, 54.10; H, 4.95; N, 11.47). The base was reduced to the corresponding secondary amine which was cyclized with formaldehyde furnishing the oily racemate of VII whose infrared spectrum was identical (40 bands) with that of (+)-VII from natural sources (Found: C, 74.77; H, 8.58. $C_{17}H_{23}NO_2$ requires: C, 74.69; H, 8.48). The racemic picrate, m.p. 209-212°, exhibited

an infrared spectrum (KBr) identical with that of (+)- VII. (Found: C, 54.68; H, 5.11; N, 11.06. $C_{23}H_{26}O_9N_4$ requires: C, 54.97; H, 5.22; N, 11.15). Gas chromatographic behavior of the two materials was identical on a 3500 theoretical plate silicone (SE-30) column.

These results lead us to speculate that if the biogenesis proceeds through a precursor such as II, it may involve an alternate mode of coupling of the two rings (cf. II ⟶ X, route B) followed by a dienone-phenol type rearrangement to either of the equivalent unsubstituted positions of ring A to yield XI, which possesses the correct arrangement of oxygen substituents. However, at present the possibility that Ar-methoxylation follows phenol coupling cannot be eliminated.

Tetrahedron Letters No.3, pp. 110-118, 1961. Pergamon Press Ltd. Printed in the United States of America.

DIE STRUKTUR DES AUCUBINS

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(Received 6 February 1961)

In kürzlichen Veröffentlichungen wurden für das Glucosid Aucubin die alternativen Formeln Ia[2,3,4,5] und Ib[4] vorgeschlagen, die beide den bis anhin erhobenen chemischen Befunden zu entsprechen scheinen. 60 MHz-Kernresonanzspektren[6,7] und ein weiterer Abbau erlauben nun, dem Aucubin eindeutig die Formel Ia zuzuweisen.

Das Kernresonanzspektrum des Hexaacetylderivates einer Struktur Ia sollte bei hoher Resonanzfeldstärke bei etwa

1 Gegenwärtige Adresse: California Institute of Technology, Pasadena, California, U.S.A.

2 S. Fujise, H. Obara & H. Uda, Chem. & Ind. 1960, 289.

3 J. Grimshaw & H.R. Juneja, Chem. & Ind. 1960, 656.

4 M.W. Wendt, W. Haegele, E. Simonitsch & H. Schmid, Helv. 43, 1440 (1960).

5 Die in der früheren Arbeit [4] gewählten Formelnummern werden in der vorliegenden Veröffentlichung beibehalten.

6 Die Spektren wurden mit einem Varian-Spektrometer in Deuterochloroform als Lösungsmittel und Tetramethylsilan als internem Standard aufgenommen.

7 Für die Aufnahme der Spektren und wertvolle Diskussionen danken wir Herrn Dr. A. Melera, Varian A.-G., Schweiz, bestens.

125 c /s.[8] die Resonanzbanden der Acetylgruppen zeigen. Die chemische Verschiebung des zur Enoldoppelbindung allylischen Protons am C-5 sollte grösser als 152 c /s sein, da ähnliche Methylenprotonen ein Signal an dieser Stelle geben[9] . Die Resonanzsignale des tert. allylischen Protons am C-9 und der übrigen Protonen sollten bei noch kleineren Feldstärken auftreten. Auf der andern Seite würde man vom Hexaacetylderivat einer Verbindung Ib ein komplexes, von der Methylengruppe C-6 stammendes Signal bei ungefähr 85 c /s erwarten können[10] . Das Signal höchster Feldstärke, das in dem bei grosser Verstärkung aufgenommenen Spektrum von Hexaacetyl-aucubin erscheint, ist eine intensive Bande bei 119-123 c /s , die den Acetylgruppen zuzuordnen ist. Das Fehlen[11)] von Signalen bei höheren Resonanzfeldstärken macht die Formel Ib unwahrschein-

8 Chemische Verschiebungen relativ zu Tetramethylsilan = 0.

9 L.M. Jackman, Applications of Nuclear Magnetic Resonanz Spectroscopy in Organic Chemistry Seite 88. Pergamon Press, London (1959).

10 L.M. Jackman, op.cit., Seite 52.

11 Bei 69 c /s (J = 7 c /s) erscheint ein schwaches Triplett mit einer einem Bruchteil eines Protons entsprechenden Intensität; dieses Signal wird der Methylgruppe des Aethanols zugeschrieben, das in kleiner Menge dem deuterierten Chloroform als Stabilisator zugesetzt ist. Auch die Signale der Methylen- und Hydroxylgruppe mit den erwarteten chemischen Verschiebungen und Intensitäten werden beobachtet. Verd. Lösungen der Aucubinderivate machen die Aufnahme der Spektren mit grosser Verstärkung notwendig, so dass die Aethanolsignale beobachtbar werden.

lich. Bei kleinerer Verstärkung erscheint die Resonanz der Acetylprotonen als unsymmetrisches Dublett, das die Anwesenheit von mehr als nur einer Art Acetylgruppen anzeigt. Im mit grosser Verstärkung aufgenommenen Spektrum treten ferner drei breite, komplexe Signale zwischen 157 und 231 c /s auf, deren Intensität je einem Proton entspricht; sie können den zwei tert. allylischen Protonen am C-5 und C-9 und dem Proton am C-5' der Glucose zugeschrieben werden. Die komplexe Natur dieser Banden ist durch Spin-Spin-Kupplung mit benachbarten Protonen bedingt. Die Methylengruppe am C-6' erscheint bei 249 c /s in Uebereinstimmung mit der von Lemieux et al[12] beobachteten chemischen Verschiebung dieser Gruppe in einfachen acetylierten Kohlehydraten. Bei 348 c /s findet sich das Signal des Vinylprotons am C-7 (relative Intensität 1), das mit den Protonen der C-Atome 6, 9 und 10 gekuppelt ist. Ein Quartett mit Zentrum bei 371 c /s , das einem Proton äquivalent ist, rührt vom Enolätherproton am C-3 her, das mit den Protonen am C-4 und C-5 kuppelt. Die Resonanzsignale der noch verbleibenden Protonen liegen zwischen 281 und 318 c /s.

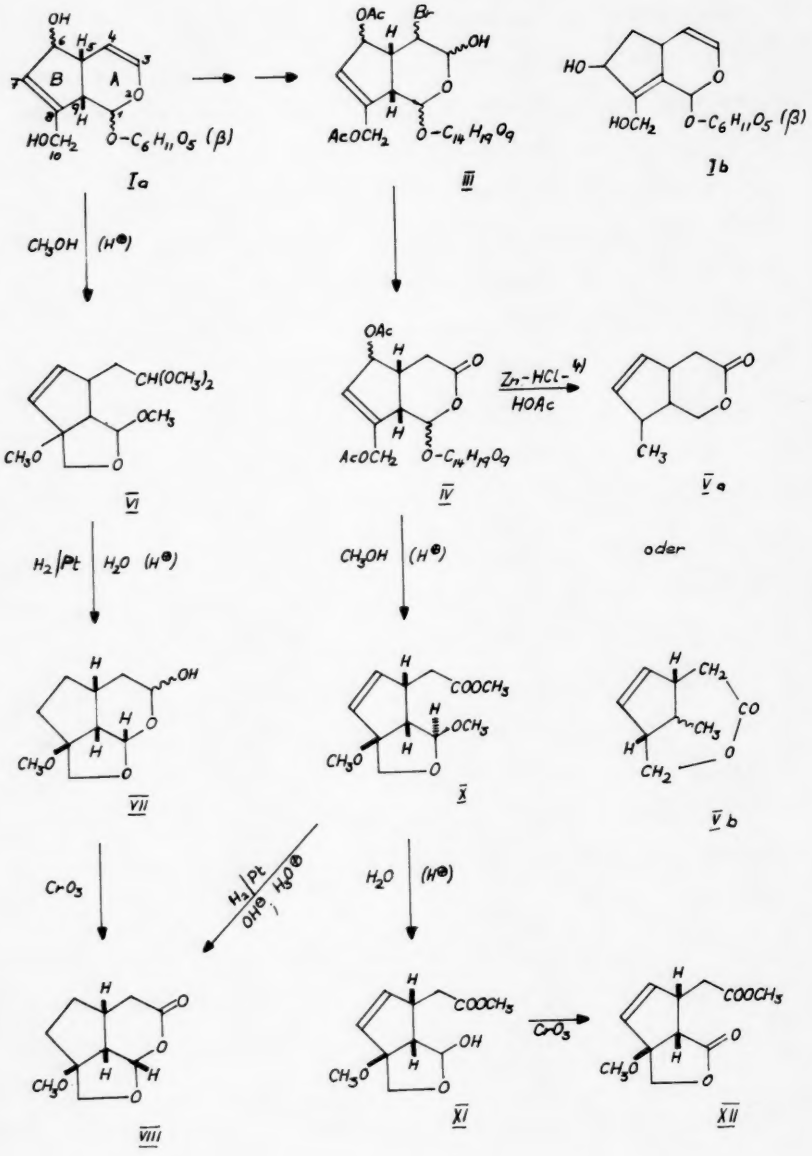
Im magnetischen Kernresonanzspektrum des aus Hexaacetyl-aucubin via III bereitbaren Laktons IV[4] ($[\alpha]_D$ -76° [$CHCl_3$]) fehlt die Bande des Enolätherprotons bei 371 c /s. Der Bereich von 281-316 c /s enthält zwei Protonen weniger als das Spektrum von Hexaacetyl-aucubin. Ein neues, einem Proton äquivalentes

12 R.U. Lemieux, R.K. Kullnig, H.J. Bernstein & W.G. Schneider, J.Amer.chem.Soc. 79, 1005 (1957).

Dublett erscheint hingegen bei 335,5 c /s (J = 3 c /s). Dieses Signal ist dem Proton am C-1 zuzuschreiben. Die chemische Verschiebung dieses Protons ist im Lakton IV grösser als im Hexaacetyl-aucubin. Aehnliche Verschiebungen sind bei korrespondierenden chemischen Aenderungen schon beobachtet worden[13] . Die Dublett-Natur der C-1-Protonenresonanz erfordert die Anwesenheit eines benachbarten Protons, was wiederum mit der Aucubin-Formel Ib im Widerspruch steht. Die Intensität der Bande bei 156 c /s ist höher als diejenige der korrespondierenden Bande im Spektrum von Hexaacetyl-aucubin und entspricht drei Protonen. Das zusätzliche Signal stammt von der neuen Methylengruppe C-4.

Durch Behandeln von IV mit 0,06 m abs. methanolischer Salzsäure erhält man nach Chromatographie und Hochvakuumdestillation bei 70-90° (Luftbad) ein einheitliches Oel X (Kontrolle durch Dünnschichtchromatographie) der Zusammensetzung $C_9H_9O_2(OCH_3)_3$ mit infraroter Carbonylbande bei 1738 cm^{-1} (CCl_4; Ester oder δ-Lakton). Das Kernresonanzspektrum zeigt die Resonanz eines Estermethoxyls bei 222 c /s und zwei Signale für die zwei andern nicht äquivalenten Methoxylgruppen bei 200 und 190 c /s ; es enthält ferner die zwei charakteristischen Quartette der beiden Vinylprotonen eines Systems R-CH=CH-CHR'R'' und die Resonanz des C-1-Protons als Singlett bei 287 c /s. Die Flächen der letztgenannten Signale entsprechen zwei resp. einem Proton.

13 H. Conroy, Advances in Organic Chemistry Vol. II, Seite 288. Interscience Publishers, New York (1960).


Ia
III
Ib
CH3OH (H⊕)
IV
Zn-HCl-HOAc
Va
oder
VI
H2/Pt H2O (H⊕)
CH3OH (H⊕)
VII
X
Vb
CrO3
H2/Pt OH⊖ ; H2O⊕
H2O (H⊕)
VIII
XI
CrO3
XII

1961

Mit verdünnter Essigsäure resultierte aus X die ölige, durch Chromatographie und Hochvakuumdestillation gereinigte Dimethoxyverbindung XI $C_9H_{10}O_3(OCH_3)_2$ (IR [CCl_4]: OH 3356 cm^{-1}, Ester 1730 cm^{-1}). Chromsäureoxydation von XI oder direkt von X in wässriger Essigsäure gab den Laktonester XII $C_9H_8O_3(OCH_3)_2$, Smp. 55-56°, $[\alpha]_D$ +214° ($CHCl_3$), der beim Erhitzen mit Methanol und nachfolgender Diazomethanbehandlung unverändert blieb (kein Anhydrid), im UV nur geringe Endabsorption und im IR (CCl_4) die Banden eines γ-Laktons bei 1792 cm^{-1} und der Estergruppe bei 1736 cm^{-1} zeigte. Bei der Laktontitration wurden 1,98 Aequivalente Lauge verbraucht. XII nahm mit Platinoxyd und Essigester 0,98 Mole Wasserstoff unter Bildung eines öligen Hydrierungsproduktes $C_9H_{10}O_3(OCH_3)_2$ auf, das nach Kuhn-Roth kein $CH_3(C)$ enthielt. Im Kernresonanzspektrum von XII erkennt man die Resonanz der beiden Vinylprotonen, die Banden der drei Protonen der Methylestergruppierung (222 c /s , 3 Protonen) und der aliphatischen Methoxylgruppe (193 c /s , 3 Protonen). Ein Signal in der Gegend von 287 c /s fehlt.

X gab durch katalytische Hydrierung (Platinoxyd in Essigester; Aufnahme 0,98 Mole Wasserstoff), Verseifung des Hydrierungsproduktes mit verdünnter Lauge und Hochvakuumdestillation der gebildeten Säure ein δ-Lakton vom Smp. 103-104°, das sich auf Grund der Mischprobe und IR-Spektren mit dem Lakton VIII, das früher aus Aucubin via VI und VII erhalten wurde, als identisch erwies. Im NMR-Spektrum von VIII wird die Resonanz des Protons am C-1 als Dublett mit Zentrum bei 345,5 c /s (J = 5 c /s)

und der aliphatischen Methoxylgruppe bei 195 c /s beobachtet. Die chemische Verschiebung des C-1-Protons in IV und VIII ist als Folge der etwas andersartigen Umgebung etwas verschieden.

Aus den obigen Ausführungen geht hervor, dass die säurekatalysierte Methanolyse von IV mit einer Allylumlagerung verknüpft ist. Die sek. Acetoxylgruppe im Geninteil musste somit ursprünglich am C-6 und nicht am C-7 des Aucubin-Gerüstes haften. Die Festlegung der Struktur von VIII erfordert eine Revision der früher[4] für das Methanolyseprodukt aus Aucubin und dessen Derivate angegebenen Formeln im Sinne der Strukturen VI und VII, da auch hier die Abspaltung der Glucose von einer Allylumlagerung im Ring B begleitet ist[14] .

Aus der Existenz von VII in der cyclischen Halbacetalform und der glatten Relaktonisierung der aus VIII mit Alkali bereiteten Hydroxysäure darf auf das Vorliegen eines nur wenig gespannten Systems in VII bezw. VIII geschlossen werden. An Modellen[15] von VII und VIII ist diese Forderung nur dann erfüllt, wenn sie die im Formelschema angeführte Konfiguration (oder ihr Spiegelbild) besitzen. Für die Kupplungskonstante des C-1-Protons lässt sich ein Wert von 5-6 c /s abschätzen[16] , in guter Uebereinstimmung mit dem gefundenen J = 5 c /s. Im NMR-Spektrum von

14 Von der Verbindung VI war für die Aufnahme eines Kernresonanzspektrums nicht mehr genügend Substanz vorhanden. Eine alternative Formulierung mit geschlossenem A- und offenem C-Ring halten wir für unwahrscheinlich.

15 Aufgebaut aus Dreiding-Stereomodellen.

16 H. Conroy, op.cit., Seite 311.

X erscheint die Resonanz des C-1-Protons als Singlett; das Zentrum C-1 muss daher die entgegengesetzte Konfiguration besitzen. Im NMR-Spektrum von XII erscheint diese Resonanz des C-9-Protons durch Kupplung mit dem Proton am C-5 als Dublett mit Zentrum bei 193 c /s ; der Wert von J = 8,4 c /s weist auf cis-Stellung[16] der beiden an den erwähnten Ringkohlenstoffen haftenden Substituenten hin. Ein Rückschluss von der Konfiguration von VIII oder X auf die Konfiguration der C-Atome 5 und 9 in Aucubin (Ia) ist nicht ohne weiteres zulässig, da bei der Umwandlung von Ia, bezw. IV in VIII, bezw. X eine Konfigurationsumkehr am C-9 nicht ausgeschlossen werden kann.

An Modellen[15] ist ersichtlich, dass trans-Verknüpfung der beiden Ringe in Ia, III und IV[17] zu einer spannungsreichen Struktur führt im Gegensatz zur cis-Verknüpfung. Das Vorliegen von III als cyclisches Halbacetal[4] spricht für cis-Verknüpfung[18] .

17 Bei der Umwandlung von Ia in IV ist eine Konfigurationsumkehr am C-9 ausgeschlossen.

18 Das Kernresonanzspektrum von IV scheint diese Annahme zu stützen. Am Modell mit trans verbundenen Ringen lassen sich für die Winkel zwischen den durch die Atome H-C-9-C-1 und C-9-C-1-H bestimmten Ebenen bei trans-Stellung der beiden H-Atome Werte von ca. 175°, bei cis-Stellung von ca. 60-65° abschätzen, die nach Conroy[16] Kupplungskonstanten von 10 c /s , bezw. 1,5 c /s ergeben würden. Die Kupplung des am C-1 haftenden Protons beträgt 3 c /s. In der flexibleren cis-Struktur lassen sich für die eine Sesselkonformation J-Werte von ca. 2 c /s , für die andere mit cisständigen H-Atomen am C-1 und C-9, d.h. mit äquatorialem H und axialer Glucosidbindung, ein J-Wert von 3 c /s abschätzen (Die Konfiguration mit trans-ständigen H-Atomen würde eine wesentlich grössere Kupplung bewirken).

Dem Schweizerischen Nationalfonds zur Förderung der wissenschaftlichen Forschung danken wir bestens für die gewährte Unterstützung.

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ON THE ABSOLUTE CONGIFURATION OF THE DITERPENE ALKALOIDS RELATED TO VEATCHINE AND ATISINE[1]

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Stanford University, Stanford, California

(Received 9 February 1961)

The recent articles by Pelletier[2,3] on the relative stereochemistry of the diterpene alkaloids of the veatchine - atisine class[4] prompt us to record some of our own results in this field. As will be shown below, our investigations establish the absolute configuration of the C/D ring juncture and by inference, the complete absolute configuration of this group of alkaloids.

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[1] Alkaloid Studies XXVIII, S. C. Pakrashi, S. K. Roy, L. F. Johnson, T. George and C. Djerassi, Chemistry & Industry in press.

[2] S. W. Pelletier, J.Amer.Chem.Soc. 82, 2398 (1960).

[3] A. J. Solo and S. W. Pelletier, Chemistry & Industry 1108 (1960).

[4] For summary see K. Wiesner and Z. Valenta in L. Zechmeister's Progress in the Chemistry of Organic Natural Products. Springer Verlag, Vienna, 1958, Vol. XVI, pp. 26-89.

Garryfoline (I)[5,6] was transformed into cuauchichicine[5] hydrochloride acetate (m.p. 265° dec., $[\alpha]_D$ -55°) and then subjected to internal Hofmann elimination[7] to afford the azomethine II, which had been obtained earlier[4,5] in much poorer yield by selenium pyrolysis of veatchine or cuauchichicine. Treatment with nitrous acid in the presence of sodium acetate[8] led in nearly quantitative yield to the hemiacetal III (m.p. 203-205°, $\lambda_{max}^{chlf.}$ 5.79 μ, $[\alpha]_D$ -128°, negative R.D. Cotton effect[9] with trough at $[\alpha]_{322.5}$ -1494° (dioxane)), which was reduced by the Wolff-Kishner procedure to the alcohol IV (m.p. 89-90°, $[\alpha]_D$ -47°). The location of the primary hydroxyl group

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[5] C. Djerassi, C. R. Smith, A. E. Lippman, S. K. Figdor and J. Herran, J. Amer. Chem. Soc. 77 4801, 6633 (1955).

[6] We are using a number system which we have proposed earlier for cafestol (C. Djerassi, M. Cais and L. A. Mitcher, J. Amer. Chem. Soc. 81, 2386 (1959)) and which has now been accepted also by Prof. L. H. Briggs for other diterpenoids of the phyllocladene group (see also ref. 13).

[7] Utilizing the conditions of D. Dvornik and O. E. Edwards, Can. J. Chem. 35, 860 (1957) in the atisine series.

[8] We are grateful to Dr. O. E. Edwards for providing us with the experimental details of a similar deamination conducted in the atisine series (O. E. Edwards and R. Howe, Proc. Chem. Soc. 62 (1959)).

[9] C. Djerassi, Optical Rotatory Dispersion: Applications to Organic Chemistry. Mc-Graw-Hill Book Co., New York 1960.

(at C-20 rather than C-19) and hence the structure of the hemiacetal III[10] was deduced from the extremely hindered nature of its corresponding aldehyde VI (vide infra) and the oxidation to the carboxylic acid V (m.p. 213-215°, $[\alpha]_D$ -40°). Through the cooperation of Dr. W. Simon,[11] the apparent dissociation constant of V was determined and found to be pK^*_{MCS} 9.49 as compared with pK^*_{MCS} 8.45 for deoxypodocarpic acid and pK^*_{MCS} 7.92 for dehydroabietic acid measured under the same conditions. This clearly eliminated C-4 as the point of attachment of the carboxyl group and the observed value of 9.49 is in reasonable agreement with the minimum value of 8.91 calculated by Simon's method[11] for V. The hindered nature of the primary hydroxyl group of IV is also evidenced by the observation that the alcohol could be eluted from neutral alumina (activity II) with hexane-benzene (1:1), while benzene-ether was required for the hemiacetal III.

Chromium trioxide - pyridine oxidation of IV furnished the aldehyde VI. Attempts to purify the crude aldehyde (m.p. 75-84°) by recrystallization or sublimation resulted in gradual conversion to the acid V. The extreme degree of steric hindrance imposed upon the aldehyde could be demonstrated by the

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[10] Structure III implies that the deamination proceeds through the double bond isomer of the azomethine II with which it is in equilibrium (see ref. 4).

[11] P. F. Sommer, V. P. Arya and W. Simon, Tetrahedron Letters No. 20, 18 (1960).

fact that its negative R.D. Cotton effect (trough at $[\alpha]_{320}$ -818° in methanol) was unaffected in the presence of hydrochloric acid, showing[9] that no acetal was produced, and that Wolff-Kishner reduction required extremely drastic conditions (3 days at 217°) to afford the hydrocarbon VII (m.p. 52°, $[\alpha]_D$ -43°), over 50% of the aldehyde VI being recovered after such treatment.

The hydrocarbon VII was not identical with either α- or β-dihydrophyllocladene, the C-16 isomeric hydrocarbons obtained by hydrogenation[12] of phyllocladene (VIII). As the relative and absolute configuration of phyllocladene (VIII) has been established,[13] garryfoline (I) and its relatives cannot possess the absolute configuration implicit in stereoformula VIII. Nevertheless, the nor-ketones IX and X derived[12,14] from phyllocladene (VIII) proved to be of importance in settling the absolute configuration of the C/D ring fusion of the diterpenoid alkaloids.

The negative rotatory dispersion Cotton effects of the ketones II and III obtained from garryfoline (I) are similar

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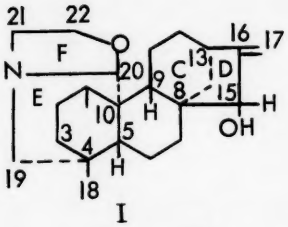
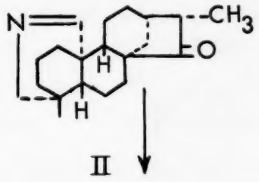
12 C. W. Brandt, New Zealand J. Sci. Techn. 20, 8B (1938).

13 L. H. Briggs, B. F. Cain and R. C. Cambie, Tetrahedron Letters No. 8, 17 (1959); P. K. Grant and R. Hodges, Tetrahedron 8, 261 (1960).

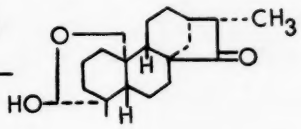
14 R. Henderson and R. Hodges, Tetrahedron 11, 226 (1960), as well as unpublished experiments by L. H. Briggs and collaborators.



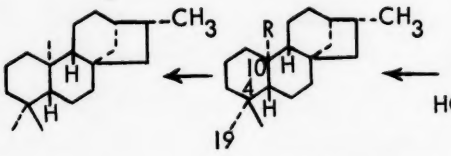
I



II

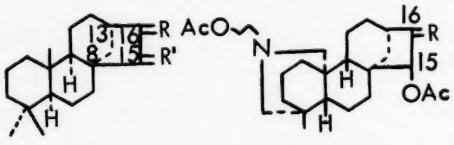


III



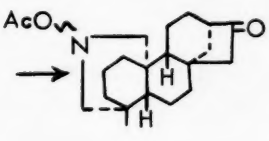
VII

IV R = CH_2OH
V R = CO_2H
VI R = CHO

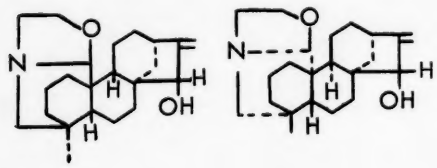


VIII R = CH_2; R' = H_2
IX R = O; R' = H_2
X R = H_2; R' = O

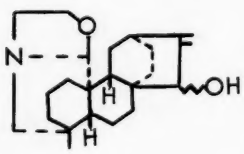
XI R = CH_2
XII R = O



XIII



XIV XV



XVI

to those observed for the 15-ketone X and other 15-ketones of the phyllocladene series. This suggests that the absolute configuration of the ring junctures at C-8 and C-13 of garryfoline (I) and phyllocladene (VIII) are identical. Further support for this supposition could be provided by oxidizing F-dihydrogarryfoline[5] diacetate (XI) (m.p. 105-106°, $[\alpha]_D$ -83°) in acetic acid solution with the osmium tetroxide-periodate reagent[15], the resulting 16-keto acetate XII (m.p. 146-147°, $[\alpha]_D$ -82°) exhibiting a positive Cotton effect (peak at $[\alpha]_{327.5}$ + 687° in dioxane solution) as does[16] the 16-ketone IX from phyllocladene. Most importantly, removal of the C-15 acetoxy group of XII with calcium in liquid ammonia provided the 16-ketone XIII (m.p. 69-70°, $[\alpha]_D$ -48°), whose positive Cotton effect was now practically superimposable upon that[16] of the phyllocladene 16-ketone IX. Since the configuration at C-9 will have no effect upon the sign of the Cotton effect, the governing factor[17] being the configuration at the ring junctions (C-8 and C-13) of the cyclopentanone ring, we can conclude safely that garryfoline (I) and phyllocladene (VIII) possess identical absolute configurations at these centers.

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[15] R. Pappo, D. S. Allen, R. U. Lemieux and W. S. Johnson, J. Org. Chem. 21, 478 (1956).

[16] C. Djerassi, R. Riniker and B. Riniker, J. Amer. Chem. Soc. 78, 6362 (1956).

[17] See J. F. Grove, J. MacMillan, T. P. C. Mulholland and W. B. Turner, J. Chem. Soc. 3049 (1960).

Furthermore, as the hydrocarbon VII has been shown to be different from the dihydrophyllocladenes, the absolute configuration of garryfoline can only be represented by I, XIV or XV. If the latter were correct, then the aldehyde VI would not be expected to exhibit the extreme degree of hindrance mentioned above, as ring B would then exist in the boat form and would thus unshield the angular aldehyde on one side. Taken in conjunction with other arguments summarized by Solo and Pelletier,[3] only absolute configuration I for garryfoline is consistent with all the experimental facts. On this basis, our hydrocarbon VII should be the antipode of one of the possible reduction products of mirene (a stereoisomer of phyllocladene (VIII)), since the latter has been attributed[18] the same relative (but opposite absolute) stereochemistry at positions 5, 8, 9, 10 and 13, as shown for VII.

Garryfoline (I) has been interrelated[4,5] with veatchine (C-15 epimer of I) and garryine. Furthermore, an experimental connection has been achieved[2] with veatchine and atisine, so that the absolute configuration XVI can now be assigned to the latter. It is pertinent to note that Dvornik and Edwards[19] have proposed earlier the possibility that the A/B

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[18] L. H. Briggs, B. F. Cain, R. C. Cambie and B. K. Davis, Tetrahedron Letters No. 24, 18 (1960).

[19] D. Dvornik and O. E. Edwards, Chemistry & Industry 623 (1958).

ring juncture in atisine (XVI) may be antipodal to that of the steroids by molecular rotation difference calculations utilizing a degradation product in which ring C became phenolic. Furthermore, it is of considerable biogenetic significance that the present absolute configurational assignments coincide with those made by x-ray analysis[20] for some of the poly-oxygenated aconite alkaloids.

All rotations were determined in chloroform solution and satisfactory elementary analyses have been secured for all substances. We are indebted to the National Heart Institute of the National Institutes of Health for financial help (grant No. H-5048) and to Professor L. H. Briggs of the University of Auckland for providing us with several specimens for comparison purposes.

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[20] M. Przybylska and L. Marion, Can. J. Chem. 37, 1843 (1959). See also F. W. Bachelor, R. F. C. Brown and G. Büchi, Tetrahedron Letters No. 10, 1 (1960).

Tetrahedron Letters No.3, pp. 127-130, 1961. Pergamon Press Ltd. Printed in the United States of America.

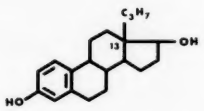
SYNTHESE STEREOSPECIFIQUE TOTALE D'UN HOMOLOGUE ANGULAIRE DE L'HORMONE FOLLICULINIQUE NATURELLE. LE 13-PROPYL NOR-ESTRADIOL

L. Velluz, G. Nominé, R. Bucourt, A. Pierdet et Ph. Dufay

Centre de Recherches Roussel-Uclaf. Paris

(Received 10 February 1961)

Un accès stéréospécifique à l'hormone folliculinique naturelle, l'estradiol, a été réalisé récemment dans notre laboratoire [1]. Sur ce même principe et par une extension comparable à celle que BACHMANN avait déjà recherchée dans la série de l'équilénine racémique [2], nous rapportons dans la présente Note la synthèse totale d'un homologue angulaire du principe sexuel féminin : le 13-propyl nor-estradiol.



13-Propyl nor-estradiol

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[1] L. Velluz, G. Nominé, J. Mathieu, E. Toromanoff, D. Bertin, M. Vignau et J. Tessier, C.R. Acad. Sc. 250, 1510 (1960).

[2] W.E. Bachmann et D.W. Holmes, J. Amer. Chem. Soc. 63, 595 et 2592 (1941).

a - L'allyl-cyanocétone, I, est hydrogénée pour former le propyle angulaire sur la future position 13, II. Par condensation sur le succinate diméthylique, on obtient l'ester cétonique, III, qui, après réduction par l'hydroborure et saponification, fournit l'acide insaturé, IVa. On dédouble à ce stade par le L(+)-thréo 1-p-nitrophényl 2-amino propane 1,3-diol et poursuit les opérations sur l'isomère lévogyre, IVb, dont nous avons établi qu'il correspondait à la série naturelle.

b - Par décarboxylation de IVb, on obtient l'éthylénique, V, dont l'hydrogénation palladiée fournit stéréospécifiquement l'alcool VIa (formiate, VIb). La réduction consécutive de cet alcool par le sodium dans l'ammoniac liquide conduit, après hydrolyse, à l'hydroxycétone conjuguée, isolée sous forme de benzoate, VII.

c - Lors de la condensation avec le 1,3-dichloro 2-butène, déjà décrite dans notre précédent travail [3], il s'est révélé ici avantageux d'activer la cétone conjuguée, VII, en formant l'ène-amine, VIII. L'hydrolyse acide du produit de condensation, IX, conduit directement à l'hydroxydione, X. La cyclisation alors assurée par le ter-amylate de sodium dans le benzène, à froid, fournit la diénone, XI, que l'on isomérise à l'aide

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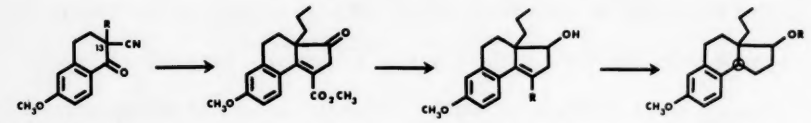
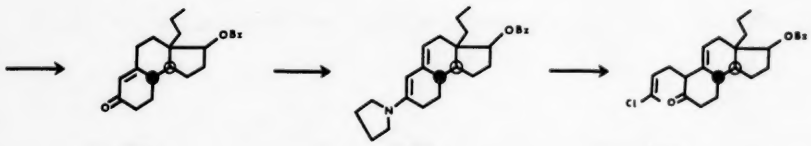
[3] L. Velluz, G. Nominé, J. Mathieu, E. Toromanoff, D. Bertin, J. Tessier et A. Pierdet, C.R.Acad.Sc. 250, 1084 (1960).



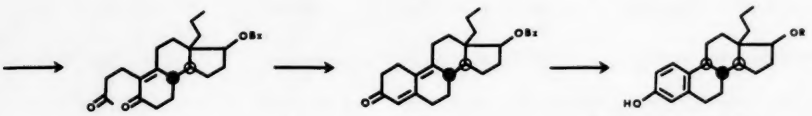
I R=CH_2-CH=CH_2 III IVa R=CO_2H, dl VIa R=H

II R=CH_2-CH_2-CH_3 b R=CO_2H, l b R=CHO

V R=H



VII VIII IX



X XI

XIIa R=COC_6H_5

XIIb R=H(solvat CH_2Cl_2)

Produits	F	$[\alpha]_D$
I	88°	
II	97°	
III	96°	
IVa	178-182° puis 196°	
IVb	213°	- 153°5 (1%, MeOH)
V	167°	- 111° (1%, MeOH)
VIb	77°	- 57°6 (1%, $CHCl_3$)
VII	112°	+ 26° (1%, MeOH)
VIII	119°	+ 138° (1%, C_6H_6)
X		+ 25° (1%, MeOH)
XI	166°	- 108°5 (0,6%, MeOH)
XIIa	214°	+ 59°6 (0,5%, EtOH)
XIIb	110°	+ 57° (0,2%, EtOH)

d'un catalyseur au palladium. On obtient, en définitive, le 17-benzoate du 13-propyl nor-estradiol, XIIa, puis le 13-propyl nor-estradiol, XIIb, sous sa forme optiquement active, exempte de tout diastéréoisomère artificiel.

Le test d'activité biologique établit que le 13β-propyl nor-estradiol est deux fois plus actif que l'hormone physiologique elle-même, l'estradiol.

Il apparaît, en bref, que si les méthodes générales que nous avons fait connaître [4] laissent entrevoir à l'industrie stéroïdienne des applications compétitives réelles, elles suggèrent d'ores et déjà la synthèse totale d'homologues pouvant surclasser en quelque sorte les hormones naturelles.

Tous les composés cristallisés décrits dans cette Note ont fourni des analyses centésimales satisfaisantes.

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[4] L. Velluz, G. Nominé et J. Mathieu, Angew. Chem. 72, 725 (1960).

Tetrahedron Letters No. 4, pp. 131-135, 1961. Pergamon Press Ltd. Printed in the United States of America.

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SOLVENT EFFECTS ON THE STEREOSELECTIVITY OF DIELS-ALDER REACTIONS[1]

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(Received 21 February 1961)

THE Alder rule states that of the two possible stereoisomeric adducts (endo and exo) of a cyclic diene with a dienophile, that one (usually endo) which is formed with the "maximum accumulation of double bonds" will preponderate.[2] The physical basis for the rule has been assumed[3] to be a lower activation enthalphy for endo-addition.

Although many examples of violations of this rule are known,[4] it has frequently not been experimentally clear whether the preponderance of the "abnormal" exo-product in these cases is the result of a kinetic preference for exo-addition or an isomerization subsequent to formation of a kinetically favored endo-adduct. Even in the cases where the product mixture is suspected to be kinetically determined, it has not been established

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1 This research was supported in part by a grant from the Petroleum Research Fund administered by the American Chemical Society. Grateful acknowledgment is hereby made to the donors of said fund. We are also indebted to the Alfred P. Sloan Foundation for support of part of this work.

2 K. Alder and G. Stein, Agnew. Chem. 50, 514 (1937)

3 A. Wassermann, J. Chem. Soc. 828, 1511 (1935); 432 (1936); 612 (1942); Trans.Faraday Soc. 34, 128 (1938); 35, 841 (1939); R.B. Woodward and H. Baer, J. Amer. Chem. Soc. 66, 645 (1944)

which of the activation parameters is responsible for the preference.

We have now investigated the effect of temperature on the kinetic ratio of stereoisomeric products in the additions of cyclopentadiene to methyl acrylate and methyl methacrylate in various solvents. Data at high temperatures were obtained with the aid of a magnetically controlled break-seal device[5] which allowed pre-heating of the addends before mixing. Control experiments showed that the product compositions were not altered by isomerization or by preferential reaction of one component with excess cyclopentadiene under the experimental conditions. Analyses were carried out by gas-liquid partition chromatography. If it is assumed that the formation of endo- and exo- products in each system follows the same rate law, the slope of the line obtained from a plot of $\log_{10}$[(endo) / (exo)] vs. 1/T may be identified with $(E_a^{exo}-E_a^{endo})/2.303R$, where E_a is an Arrhenius activation energy, and the intercept with $\log_{10}(A^{endo}/A^{exo})$, where A is a pre-exponential term. The results are shown in Table I. The uncertainties are estimated from the reproducibilities of replicate runs, in which the variation of the absolute value of the % of a given component was less than 0.25%.

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[4] For summaries of references, see J.A. Berson, R.D. Reynolds and W.M. Jones, J. Amer. Chem. Soc. 78, 6049 (1956), and K. Alder, R. Hartmann and W. Roth, Liebigs Ann. 613, 6 (1958). See also J.S. Meek and W.B. Trapp, J. Amer. Chem. Soc. 79, 3909 (1957); W.R. Boehme, E. Schipper, W.G. Scharpf and J. Nichols, J.Amer. Chem. Soc. 80,5488 (1958); M. Schwarz and M. Maienthal, J. Org. Chem. 25, 449 (1960).

[5] Designed by Mr. Allen Remanick of this laboratory.

TABLE I

Dienophile	Solvent	Temp. Range (°C)[a]	$\log_{10}(A^{endo}/A^{exo})$	$(E_a^{exo} - E_a^{endo})$ kcal. / mole
Methyl acrylate	decalin	-35 to + 170	+ 0.28 ± 0.02	+ 0.36 ± 0.04
Methyl acrylate	acetone	0 to + 56	+ 0.08 ± 0.08	+ 0.73 ± 0.11
Methyl acrylate	CH_3CN	0 to + 66	+ 0.13 ± 0.02	+ 0.78 ± 0.04
Methyl acrylate	MeOH	0 to + 56	- 0. 2 ± 0. 1	+ 1.48 ± 0.13
Methyl methacrylate	decalin	+56 to + 139	+ 0.20 ± 0.05	- 0.71 ± 0.03
Methyl methacrylate	acetone	0 to + 56	- 0.01 ± 0.05	- 0.34 ± 0.08
Methyl methacrylate	CH_3CN	0 to + 66	- 0.12 ± 0.05	- 0.40 ± 0.08
Methyl methacrylate	MeOH	0 to + 56	- 0. 3 ± 0.15	+ 0.08 ± 0.08

[a] Data for methyl acrylate in decalin were obtained at five different temperatures, for all others, at three different temperatures. Plots of $\log_{10}$ [(endo)/(exo)] vs. 1/T were nicely linear in all cases.

With both dienophiles, a change to more polar solvent favors endo-addition in the enthalpic sense; a trend in the opposite direction obtains in the pre-exponential terms, where the preference for endo-addition is decreased in more polar solvent.

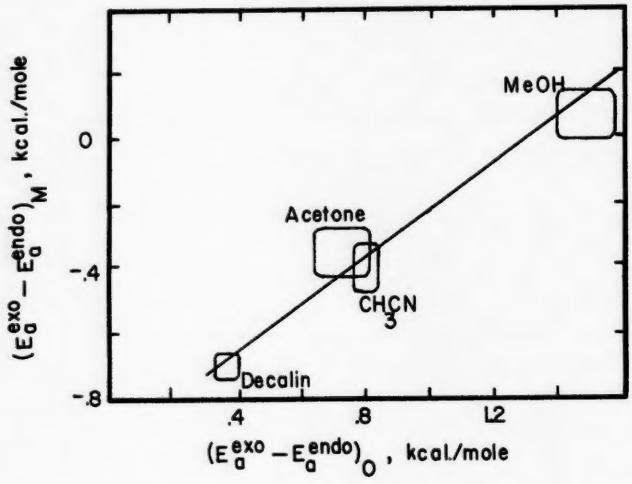


Fig. 1

Within the limited series studied, the solvent effects can be correlated approximately linearly in the enthalpy differences (Fig. 1) by an equation of the form

$$(E_a^{exo} - E_a^{endo})_M = (E_a^{exo} - E_a^{endo})_O + C$$

where M and O refer to methyl methacrylate and methyl acrylate respectively. The correlation slope, $\mu \cong 0.75$, suggests that the enthalpic stereoselectivity for methyl methacrylate is slightly less sensitive to solvent change than that for methyl acrylate. Further work is required to determine whether this kind of correlation holds for other solvents and dienophiles.

The range of enthalpic stereoselectivity produced by a change of solvent for a given dienophile is comparable in magnitude to that produced by a change of dienophile in given solvent; e.g. $(E_a^{exo} - E_a^{endo})_O$ in MeOH is greater than $(E_a^{exo} - E_a^{endo})_O$ in decalin by about 1.1 kcal /mole, while $(E_a^{exo} - E_a^{endo})_M$ in decalin differs from $(E_a^{exo} - E_a^{endo})_O$ in decalin by about 1.1 kcal /mole. It seems likely, therefore, that with some dienophiles, conformity with or violation of the Alder rule (in its enthalpic sense) will be determined by the solvent. This is already very nearly the case with methyl methacrylate. Furthermore, whatever the role of the "maximum accumulation of double bonds" in the present cases, this influence competes with those exerted by solvent and structural effects and may even be overshadowed by them.

Tetrahedron Letters No.4. pp. 136-139, 1961. Pergamon Press Ltd. Printed in the United States of America.

KATALYSIERTE HOMOLOGISIERUNG CYCLOALIPHATISCHER KETONE MIT DIAZOÄTHAN

Eugen Müller, Martin Bauer und Wolfgang Rundel

Chemisches Institut der Universität Tübingen

(Received 8 February 1961)

VOR kurzem haben wir in dieser Zeitschrift[1] über die katalysierte Homologisierung cycloaliphatischer Ketone mit Diazomethan berichtet. Im folgenden teilen wir Ergebnisse mit, die wir bei der Durchführung der gleichen Reaktion, aber mittels Diazoäthan, unter Bildung α-methyl-verzweigter Homoketone erhalten haben.

Die Umsetzung von Ketonen mit Diazoäthan ist schon länger bekannt. Giraitis und Bullock[2] sowie Adamson und Kenner[3] erhielten aus einigen aliphatischen Ketonen und aus Cyclohexanon sowohl nach der "ex situ" - wie der "in situ" - Methode die methyl-verzweigten Homoketone. Eine Ubertragung dieser Reaktion auf höhergliedrige Ringketone wie z.B. das Cyclooctanon gelang den Autoren jedoch nicht.

Zur Prüfung unserer Methode setzten wir zunächst das Cycloheptanon unter $AlCl_3$-Katalyse mit Diazoäthan um. Man erhält sehr glatt und einfach

[1] E.Müller, M.Bauer und W.Lundel, Tetrahedron Letters No.13, 30 (1960).

[2] A.P.Giraitis und J.L.Bullock J.Amer.Chem.Soc. 59, 951 (1937); auch E.Mosettig und A.Burger, Ibid. 52, 3456 (1930) erwahnen den moglichen Einsatz von Diazoäthan unter Methanolkatalyse

[3] D.W. Adamson und J. Kenner, J.Chem.Soc. 181 (1939)

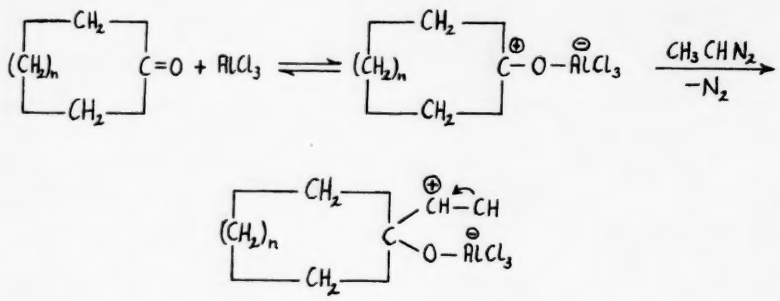
das α-Methyl-cyclooctanon in einer Ausbeute bis zu 82%, bezogen auf das eingesetzte Ausgangsketon. Dieses gute Ergebnis veranlasste uns, nunmehr weitere cycloaliphatische Ketone mit 8-14 Ringgliedern dieser Homologisierung zu unterziehen.

In der nachstehenden Tabelle sind die Versuchsergebnisse kurz zusammengestellt:

Ausgangs-keton	mMol Keton/ mMol CH_3CHN_2	Ausbeute an methyl-verzweigtem Homoketon in %	
		gaschromatographisch	destillativ
C_7	50/90	82	
C_8	50/180	57	57
C_9	50/100	72	
C_{10}	50/100	57	
C_{11}	50/100	63	
C_{12}	50/100	66	
C_{13}	50/100	60	
	200/380		55
C_{14}	20.4/40	63	

Als Katalysator hat sich wiederum Aluminiumchlorid bewährt, während Bortrifluoridätherat unwirksam ist.

Die Ausbeuten liegen hier zwischen 57 und 82%, sind also deutlich höher als bei der analogen Reaktion mit Diazomethan. Dies lässt sich auf eine induktive, stabilisierende Wirkung der Methylgruppe auf das bei der Umlagerung auftretende Carbeniumion zurückführen.



Ein weiterer Faktor ist schliesslich in einem sterischen Einfluss der Methylgruppe auf die Weiterreaktion des methylverzweigten Homoketons zu suchen, denn die Ausbeuten an höheren Homologisierungsprodukten sind sehr gering, d.h. das methylverzweigte Keton zeigt eine viel geringere Reaktionsbereitschaft als das noch vorhandene Ausgangsketon. Für diese Annahme sprechen auch Versuche über die katalysierte Homologisierung α-methylverzweigter Ketone mittels Diazomethan. So erhält man ausgehend vom α-Methylcyclononanon mit Diazomethan etwa 28 % α-Methylcyclodecanon[4] gegen 42-45% beim unverzweigten C_9-Keton, und vom α-Methyl-cyclotetradecanon das α-Methyl-cyclopentadecanon nur in Ausbeuten von etwa 20-22 % gegenuber 28.5% Cyclopentadecanon aus Cyclotetradecanon. Berücksichtigt man den statistischen Effekt bei dieser Homologisierung, d.h dass im Falle der unverzweigten Ringketone der Umlagerungsreaktion zwei gleichartige $-CH_2-$Reste zur Verfügung stehen, beim α-methyl-verzweigten dagegen nur ein $-CH_2-$Rest neben einem $-CH(CH_3)-$Rest, so sind die Ausbeuten doch noch als recht gut anzusehen.

Ob ein Effekt der Ringgrösse hinzukommt, lässt sich noch nicht entscheiden.

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[4] Vermutlich enthält diese Substanz noch etwas β-Methyl-cyclodecanon.

Bei den bisher durchgeführten Versuchen dieser Art haben wir nur wenig β-methylverzweigtes Homoketon[5] auffinden können, eine Reaktion, die beim α-Methyl-C_{14}-Ringketon zum natürlichen inaktiven Moschus führt. Eine α-ständige Methylgruppe drängt offensichtlich die Umlagerungsreaktion weitgehend in die Richtung zur Wanderung des unsubstituierten $-CH_2$-Restes.[3,6]

Die neuen α-methylverzweigten Homoketone wurden z.T. gaschromatographisch, z.T. destillativ getrennt und untersucht. Analysen, Molekulargewichtsbestimmungen und 2,4-Dinitrophenylhydrazone sowie I.R.-Spektren bestätigen die Richtigkeit der obigen Angaben.

Auch ungesättigte cycloaliphatische Ketone, wie das Δ^4-Cholestenon-3 lassen sich katalytisch mit Diazoäthan homologisieren, wobei sich nach unseren bisherigen Befunden der Äthylidenrest zwischen die Carbonylgruppe und die Doppelbindung einschiebt. Die Reaktion ist auch auf aliphatische Ketocarbonsäureester wie z.B. Lävulinsäureester anwendbar, eine Reaktion, die sich übrigens auch mit Diazomethan ausführen lässt.

Abschliessend sei noch erwähnt, dass sich auch Diazoessigester in die katalytische Homologisierungsreaktion einsetzen lässt. Die Einzelheiten dieser und der oben beschriebenen Reaktionen veröffentlichen wir an anderer Stelle.

Die Durchführung der Reaktion geschieht in der gleichen Weise wie sie beim Diazomethan beschrieben wurde.

Der Deutschen Forschungsgemeinschaft danken wir für die Unterstützung dieser Arbeit.

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[5] Über die Natriumhydrogensulfitverbindung.

[6] C.D. Gutsche, J.Amer.Chem.Soc. 71, 3513 (1949).

[7] W.S. Johnson, M. Neeman und S.P. Birkeland, Tetrahedron Letters No.5, 1 (1960) berichten über eine gleichartige Homologisierung mit Diazomethan.

Tetrahedron Letters No. 4, pp 140-142, 1961. Pergamon Press Ltd. Printed in the United States of America.

ON THE MECHANISM OF THE DEHYDROBROMINATION OF α,α,α',α'-TETRABROMO-o-XYLENE

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(Received 3 February 1961)

It was reported recently[1] that α,α,α',α'-tetrabromo-o-xylene(I) reacts with excess potassium t-butoxide to yield a mixture of 5,10-dibromobenzo[b] biphenylene(II) and 1,2,5,6-tetrabromo-3,4:7,8-dibenzotricyclo[4,2,0,$0^{2,5}$] octadiene(III). In interpreting this remarkable transformation, the reasonable suggestion was made that II and III arise via 1,2-dibromobenzocyclobutadiene(IV), the dehydrobromination product of 1,1,2-tribromobenzocyclobutene (V). The unknown tribromide V was not isolated in this reaction but its formation from tetrabromide I certainly could be postulated, via the intermediary production of the quinoid tribromide VI. Evidence now has been gathered that neither tribromide V nor the cyclobutadiene IV is involved in the conversion of I to II and III.

The bromination of trans-1,2-dibromobenzocyclobutene(VII) by N-bromosuccinimide (NBS) gave, after two days, 1,1,2,2-tetrabromobenzocyclobutene (VIII), m.p. 117-118°, in 65% yield.[2] By fractional distillation and crystallization of an incompletely brominated reaction mixture, a small amount of 1,1,2-tribromobenzocyclobutene(V), m.p. 40-41°, was obtained.

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[1] F. R. Jensen and W. E. Coleman, Tetrahedron Letters No. 20, pp. 7-11, 1959.

[2] All new compounds gave satisfactory analyses for the formulae assigned.

Tribromide V was produced also rapidly and in good yield (72%) by treatment of cis-1,2-dibromobenzocyclobutene[3] (IX), m.p. 101-101.5°, with one equivalent of NBS. The structure of tetrabromide VIII was proven by its reaction with silver trifluoroacetate to give benzocyclobutenedione[4] (X) in 41% yield. The dehydrobromination of tribromide V with potassium t-butoxide gave none of compounds II and III, but rather an 85% yield of the orange 5,6-dibromobenzo[a]biphenylene (XI), m.p. 149-150°. The biphenylene derivative XI was obtained as well, in 41% yield, by sodium iodide treatment of 1,1,2,2,tetrabromobenzocyclobutene (VIII). The intermediary 1,2-dibromobenzocyclobutadiene (IV) thus undergoes not linear dimerization, but the previously observed type of angular dimerization.[5,6] The postulated immediate precursor of XI, the tetrabromide XII, could be synthesized in 68% yield as colorless crystals, m.p. 155-155.5°, by addition of bromine to XI. As predicted, XII lost bromine rapidly under the influence of potassium t-butoxide to regenerate the orange bromide XI.[7]

As a result of the above observations, we suggest tentatively that tetrabromo-o-xylene is dehydrobrominated by strong base to the quinoid bromide VI; instead of undergoing intramolecular cyclization to a benzocyclobutene, VI dimerizes to the dibenzocyclooctadiene derivative XIII.

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[3] F. R. Jensen and W. E. Coleman, American Chemical Society Meeting, April, 1958. Abstracts of Papers, p. 79 N.
[4] M. P. Cava and D. R. Napier, J. Am. Chem. Soc. 79, 3606 (1957).
[5] M. P. Cava and D. R. Napier, J. Am. Chem. Soc. 79, 1701 (1957).
[6] M. P. Cava and J. F. Stucker, J. Am. Chem. Soc. 79, 1706 (1957).
[7] The confirmation of the structure of compound XI by direct synthesis from a derivative of benzo[a]biphenylene will be described in the full publication. This work is omitted here for the sake of brevity.

Reasonable paths can be envisaged from XIII to Jensen and Coleman's compounds II and III. Attempts to confirm this mechanism are in progress.

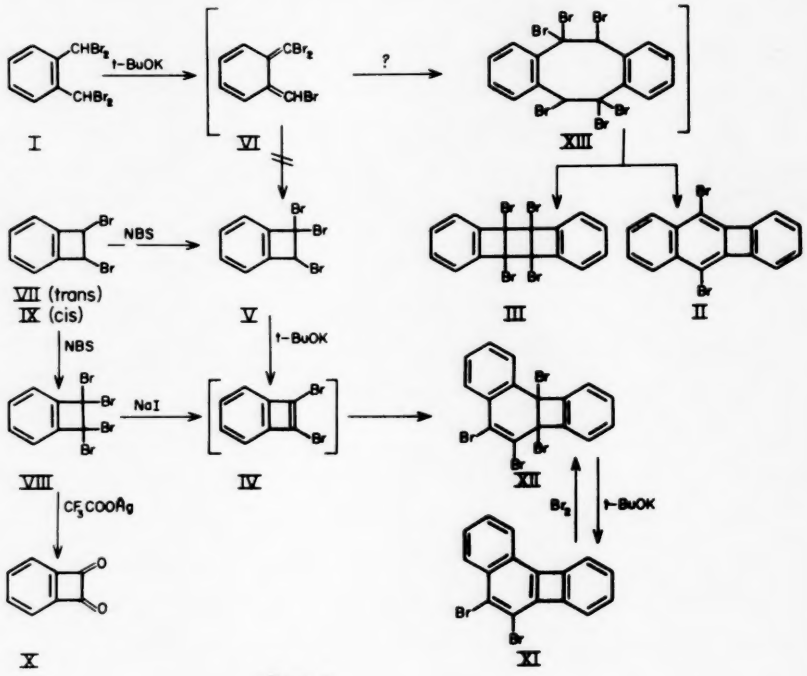

Chart 1

The support of this work by the National Science Foundation is gratefully acknowledged.

Tetrahedron Letters No. 4, pp. 143-145, 1961. Pergamon Press Ltd. Printed in the United States of America.

VINYLATION OF TRI-n-BUTYLTIN HYDRIDE

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(Received 7 February 1961)

During the course of an investigation of the reactions of acetylene with various reagents which are capable of generating free radicals, it was observed that tri-n-butyltin hydride added smoothly to acetylene. The product was tri-n-butylvinyltin, obtained in 75-80% yields (1). The reaction was conducted in benzene in an autoclave under 150-200 p.s.i.g. pressure of acetylene. A relatively mild reaction temperature of 75-80° was sufficient to initiate the reaction.

$$(n\text{-}C_4H_9)_3SnH + C_2H_2 \xrightarrow{\text{AIBN}} (n\text{-}C_4H_9)_3SnCH = CH_2 \qquad (1)$$

Tri-n-butylvinyltin has been prepared [1,2] by treating tri-n-butyltin chloride with excess vinylmagnesium bromide and by treating bis-tributyltin oxide with vinylmagnesium chloride. However, the present method has not been previously reported. It constitutes one of the few successful additions to unsubstituted acetylene to produce a vinyl derivative rather than a bis adduct.

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1. D. Seyferth and F. G. Stone, J. Am. Chem. Soc. 79,515 (1957)

2. S. D. Rosenberg, A. J. Gibbons and H. E. Ramsden, J. Am. Chem. Soc. 79, 2137 (1957).

The structure of tri-n-butylvinyltin was shown by boiling point, infra-red spectrum, nuclear magnetic resonance spectrum and elemental analysis.

A typical experiment was carried out in the following manner: A solution of 0.076 mole of tri-n-butyltin hydride, prepared from the chloride according to the procedure of van der Kerk[4], in 57 ml of dry, thiophene-free benzene, was placed in a standard, 300 ml stainless steel Aminco autoclave and 0.21 g of azobisisobutyronitrile was added. The autoclave was sealed, evacuated and purged three times with dry nitrogen and pressured to 155 p.s.i.g. with acetylene. It was heated to 80° with rocking for 30 minutes, cooled, the pressure released, and the contents charged to a distillation flask. The benzene was removed under vacuum, 1% hydroquinone was added to the residue, and 0.0615 mole of tri-n-butylvinyltin was collected as a colorless liquid, b.p. 88°/0.8 mm (literature[1,2] b.p. is 98°/1.5 mm and 114°/3 mm). The tin hydride absorbed strongly at 1810 cm.$^{-1}$ in the infra-red; the vinyl derivative had no absorption in this region, but showed absorption peaks at 943, 1007, 1900 and 3070 cm $^{-1}$ and weak absorption at 1650, all characteristic of a vinyl group. The NMR spectrum unequivocally identified the protons from the three butyl groups and differentiated them from those of the vinyl group. Peak areas were in the correct ratio of 9:1.

Anal. Calcd. for $C_{14}H_{30}Sn$: C, 53.03; H, 9.54.

Found: C, 53.13; H, 9.49.

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3. G. Gruettner, Ber. 50, 1812 (1917).

4. G. J. M van der Kerk, J. G. Noltes and J. G. A. Luijten, J. Applied Chem. 7, 366 (1957).

There was obtained as by-product in the reaction a clear mobile liquid which could not be distilled. It was at first believed to be the hexakis tin compound that would arise from coupling of two tri-n-butyltin radicals (2).

$$2(n\text{-}C_4H_9)_3Sn\cdot \longrightarrow (n\text{-}C_4H_9)_3SnSn(n\text{-}C_4H_9)_3 \qquad (2)$$

However, the corresponding hexaisobutylbistannane boils[3] at 179°/3.5 mm without decomposition. The n-butyl compound should boil close to the iso derivative. Several attempts were made to distill the high boilers, but no distillate could be collected at 200° and 0.05 mm. Higher temperatures caused decomposition. When the azo initiator concentration was raised from 1% to 2%, the yield of vinyl monomer dropped from 81% to 55% with a corresponding increase in the undistillable high boilers. The latter are therefore believed to consist of polymers of the vinyl tin derivative.

Investigation of other trisubstituted tin compounds with acetylene and a variety of catalysts and conditions is in progress.

Tetrahedron Letters No. 4, pp. 146-147, 1961. Pergamon Press Ltd. Printed in the United States of America.

A NOVEL SYNTHESIS OF BICYCLO (3·2·1)-3-OCTEN-2-OL

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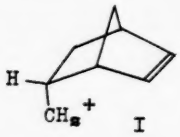
(Received 7 February 1961)

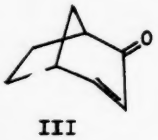
The abundance of rearrangements and non-classical ions implicit in the chemistry of bicyclo(2.2.1)heptane systems inspired an investigation of reactions involving the carbonium ion I and the corresponding exo isomer. We have investigated the gross features of one such reaction and have uncovered a novel rearrangement. Acetolysis at ca. 100° of the mixture of p-toluenesulfonate esters of the commercially available 2-hydroxymethylbicyclo(2.2.1)hept-5-ene led to a complex mixture in which the acetate IIa was the main component.



I

II

(a, X=OAc; b, X=OH)



III

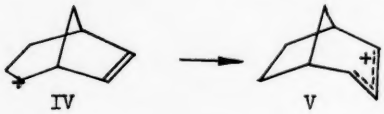
The structure of this compound is based on the evidence presented below. Fractional distillation of the solvolysis product gave IIa, b.p. 88.5-89°/11 mm , n_D^{25} 1.4807 (Found: C, 72.49; H, 8.59). Cleavage of the ester with lithium aluminum hydride in ether gave an alcohol (IIb)

whose properties were in agreement with those of a product assigned this structure by Wildman and Saunders;[1] p-nitrobenzoate, m.p. 84-85° (lit.[1] m.p. 81-81.5°), phenylurethan, m.p. 125-127° (lit.[1] m.p. 126-126.5°).

The allylic nature of the hydroxyl function was demonstrated by facile oxidation of the alcohol with manganese dioxide to an α,β -unsaturated ketone (III), b.p. 98.5°/20 mm λ max 227 mμ (ethanol), logϵ 3.9 (lit.[1] λ max 227 mμ, log ϵ 3.9); 2,4-dinitrophenylhydrazone, m.p. 140-142° (Found: C, 55.05; H, 4.73; N,18.96).

The trans stereochemistry of the product was inferred from the absence of infrared absorption at 1015 cm^{-1} in the spectrum of the bicyclo(3.2.1)octan-2-ol[2] obtained on catalytic reduction with hydrogen and palladium-charcoal.

This unusual rearrangement can best be rationalized by assuming the intervention of ion IV which could rearrange further to the allyl carbonium ion V. Attack of solvent from the exo side[2] would lead to the observed product.



IV V

[1] W. C. Wildman and D. R. Saunders, J. Amer. Chem. Soc. 76, 946 (1954).

[2] H. A. Youssef, M. E. Baum and H. M. Walborsky, J. Amer. Chem. Soc. 81, 4709 (1959).

Tetrahedron Letters No. 4, pp. 148-150, 1961. Pergamon Press Ltd. Printed in the United States of America.

PHOTOCHEMICAL REACTION OF BENZENE WITH DIMETHYL ACETYLENEDICARBOXYLATE[1]

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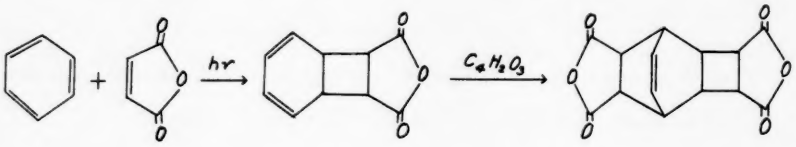
Atlanta, Georgia

(Received 8 February 1961)

The photochemical reaction of benzene with maleic anhydride has been shown to give an adduct of structure II[2,3]. This reaction evidently proceeds[1] by a photochemically activated 1,2-addition to give intermediate I followed by a 1,4-addition of maleic anhydride to give II. Similar photo-



I II

chemical reactions of maleic anhydride appear to occur with toluene, o-xylene, and chlorobenzene, especially in presence of a photosensitizer such as benzophenone[4]. We now wish to report a photochemical reaction of benzene with dimethyl acetylenedicarboxylate.

Irradiation at room temperature of a solution of dimethyl acetylenedicarboxylate (5.0 ml) in benzene (300 ml) with ultraviolet light for

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[1] This research was supported by the Office of Ordnance Research, U. S. Army.

[2] H. J. F. Angus and D. Bryce-Smith, Proc. Chem. Soc. 326 (1959); J. Chem. Soc. 4791 (1960).

[3] E. Grovenstein, Jr. and D. V. Rao, J. Amer. Chem. Soc. in press.

[4] G. O. Schenck and R. Steinmetz, Tetrahedron Letters No. 21, 1 (1960).

47 hours in a quartz apparatus previously described[5] gave, in addition to a difficulty volatile residue, 0.56 g. of yellow crystals (m.p. 109.4-110.4°. Found: C, 65.39; H, 5.35; sapn. equiv., 107; mol. wt., 254. Calcd. for $C_{12}H_{12}O_4$: C, 65.43; H, 5.49; sapn. equiv., 110; mol. wt., 220). This methyl ester was purified by crystallization from methanol and sublimation at a bath temperature of 102° and a pressure of 0.03 mm. Saponification of the ester gave an acid which after recrystallization from water was isolated as yellow crystals of m.p. 206.5-208° (dec.) (Found: C, 62.34; H, 4.18. Calcd for $C_{10}H_8O_4$: C, 62.50; H, 4.20). The acid sublimed at a bath temperature of 190° and a pressure of 0.05 mm. The acid and the methyl ester readily decolorized a solution of potassium permanganate. The acid in acetic acid solution with a 5% Pt on carbon catalyst at room temperature and atmospheric pressure absorbed 3.0 moles of hydrogen per mole of acid in 4 hours and 0.6 additional moles in 91 hours. The acid in ethanol had ultraviolet absorption (shoulder) at 300 mμ (log ε = 2.84) and a maximum at 227 mμ (log ε = 4.20). The color of the acid and its ultraviolet absorption spectrum are similar to those reported for cycloöctatetraenecarboxylic acid which has λ_{max}^{EtOH} 306 mμ (log ε = 2.92) and end-absorption at 220 mμ with log ε = 4.3. Also the infrared absorption spectra of the acid and its methyl ester are similar to those reported for cycloöctatetraenecarboxylic acid and its methyl ester (note especially that the acid has C=C absorption at 6.14 μ while absorption at longer wavelength is expected for planar conjugated olefinic bonds or an aromatic ring). Moreover cycloöctatetraenecarboxylic acid rather rapidly absorbs three molar equivalents of hydrogen and more slowly absorbs a fourth molar equivalent upon hydrogenation overa platinum

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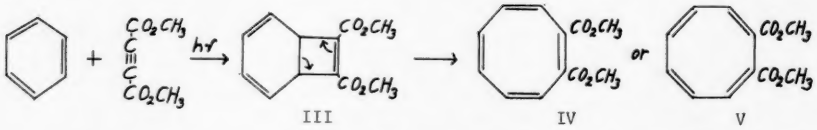
[5] E. Grovenstein, Jr. and S. P. Theophilon, J. Amer. Chem. Soc. 77, 3795 (1955).

catalyst in acetic acid solution[6].

The similarity in physical and chemical properties of the acid from reaction of benzene with dimethyl acetylenedicarboxylate with the known cyclo̤ctatetraenecarboxylic acid and the lack of similarity with phenylmaleic and phenylfumaric acids strongly implies that the photochemical product has the structure IV and /or V of dimethyl cyclo̤ctatetraene-1,2-dicarboxylate. A structure of this type can be formed by way of an intermediate III resembling that (II) proposed for the photochemical reaction of benzene with maleic anhydride. Intermediate III, however, undergoes isomerization to IV or V which is expected to be thermodynamically more stable than II and to be comparatively unreactive toward dimethyl acetylenedicarboxylate at room temperature[7].



III IV V

D. Bryce-Smith has kindly informed us that he has obtained 1 to 1 photo-adducts of acetylene derivatives with benzene etc. and that these appear to be derivatives of cyclo̤ctatetraene. Moreover G. Büchi has considered a substituted cyclo̤ctatetraene as one of several possible structures for a photo-adduct derived from benzonitrile and an acetylene derivative[9].

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[6] A. C. Copé, M. Burg and S. W. Fenton., ibid. 74, 173 (1952).

[7] Note that no appreciable amount of bicyclo[4.2.0]octa-2,4,7-triene appears to be in equilibrium with cyclo̤ctatetraene. A temperature of 160-170° was used to effect reaction between cyclo̤ctatetraene and diethyl acetylenedicarboxylate (W. Reppe, O. Schichting, K. Klager and T. Toepel, Ann. 560 1 (1948).

[8] D. Bryce-Smith, personal communication.

[9] G. Büchi, Seventh Reaction Mechanisms Conference, University of Chicago, Sept. 5, 1958.

Tetrahedron Letters No. 4, pp. 151-155, 1961. Pergamon Press Ltd. Printed in the United States of America.

THE CHEMICAL CONSTITUTION OF RUBROFUSARIN

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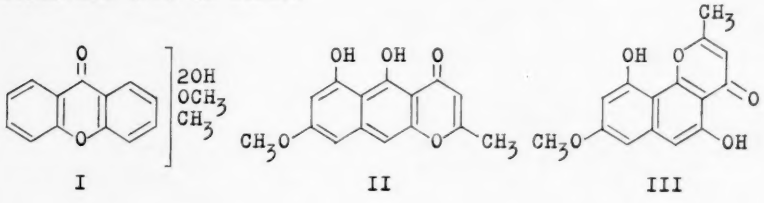
Faculty of Agriculture, Nagoya University, Anjo, Japan

(Received 10 February 1961)

RUBROFUSARIN, $C_{15}H_{12}O_5$, was first isolated as a red pigment from the mycerium of Fusarium graminearum and F. culmolum by Ashley et al.[1], who proposed its structure as a methyltrihydroxyxanthone monomethyl ether (I) mainly from its general properties. Although further investigations have been performed by other workers[2,3], its orientation has not been determined and no degradation study has been reported.

We now wish to report our finding that rubrofusarin is not the proposed methylxanthone, but is a derivative of 2-methylnaphtho-γ-pyrone and should be represented either by structure (II) or (III).



I II III

1 J.N.Ashley, B.C.Hobbs and H.Raistrick, Biochem. J. 31, 385 (1937).

2 R.P.Mull and F.F.Nord, Arch. Biochem. and Biophys. 4, 419 (1944).

3 N.A.Lund, Alexander Robertson and W.B.Whalley, J. Chem. Soc. 2434 (1953).

When rubrofusarin[4] was subjected to zinc dust distillation, naphthalene and a little anthracene were obtained, whereas no methylxanthene was detected. In connection with this fact, we have examined whether methylxanthones can give these polycyclic compounds or not, on that condition. The investigated samples were the four methylxanthone isomers and nor-lichexanthone[5]. From this zinc dust distillation study it was derived that anthracene is yielded from the xanthone[6] having a methyl group at the o-position to the carbonyl group, and that no naphthalene is afforded from any of the xanthones examined. Accordingly, we can assume the existence of a naphthalene nucleus in rubrofusarin.

The evidence for this assumption is further supplied by the alkaline degradation study of nor-rubrofusarin (i.e. demethylrubrofusarin). It was hydrolysed by refluxing for two hours with 20% aqueous sodium hydroxide in an atomosphere of nitrogen to give a naphthol[7] (IVa) in addition to acetone and acetic acid. IVa failed to crystallise owing to its in-

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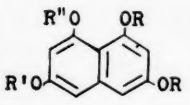
4 The pigment was obtained from the dried mycerium of F. graminearum as reddish orange prisms, m.p. 213°, in 0.25% yield.

5 (=1-Methyl-3,6,8-trihydroxyxanthone). Y.Asahina and H.Nogami, Bull. Chem. Soc. Japan 17, 202 (1942).

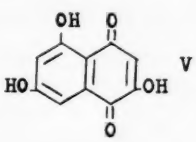
6 1-Methylxanthones may be regarded as a o-methylbenzophenone analogue. By analogy with a Elbs reaction the formation of anthracene as a main zinc dust distillate can be explained.

7 The naphthol (IVa) shows λ_{max} 242.5, 306, 318, 327 and 332 mμ ($\log\epsilon$ 4.68, 3.73, 3.76, 3.75 and 3.78 resp.), and gives an intense brown ferric reaction.

stability in air. It shows a considerable pH depression with boric acid and resists complete methylation with diazomethane. (The trimethyl ether (IVb), m.p. 141.5°, which gave a monoacetate, m.p. 107°.) A colourless alkaline solution of IVa on standing changed violet undergoing immediate aerial oxidation. In several hours, with an increase of a violet colour and a decrease of a bluish green fluorescence, the oxidation of the solution was advanced and it gave an amorphous red quinone on acidification. The quinone has an ultraviolet spectrum closely resembling that of flaviolin[8] (V) and appears to be identical with V. λ_{max} 268, 313, 384 and 462 mμ. IVa was characterized as the tetraacetate (IVc), m.p. 134° (Found: C, 59.90; H, 4.79; Ac, 49.2. $C_{18}H_{16}O_8$ requires: C, 60.00; H, 4.48; Ac, 48.0), λ_{max} 228, 286 mμ (log ε 4.89, 3.77 resp.). Ozonolysis of IVc, followed by hydrolysis, gave 3,5-dihydroxyphthalic acid, which was identified as the dimethyl ether[9]. The above results and biogenetical considerations led us to presume that the naphthol (IVa) is 1,3,6,8-tetrahydroxynaphthalene. This has been established by the



IVa, R=R'=R"=H
b, R=R'=CH_3, R"=OH
c, R=R'=R"=Ac
d, R=R"=Ac, R'=OCH_3



V

8 B.D.Astill, J. Chem. Soc. 3302 (1953).

9 The authentic sample was kindly supplied by Dr. Y. Hatsuda, Tottori University.

preparation of 1,3,6,8-tetraacetoxynaphthalene (IVc), m.p. 137°, from chromotropic acid by alkali fusion[10] and subsequent acetylation with acetic anhydride and pyridine. As expected, zinc dust distillation of IVa and IVc gave only naphthalene.

Thus it is evident that rubrofusarin has a naphthalene nucleus. According to the English workers[1,3], rubrofusarin has a C-methyl group in addition to an unreactive carbonyl group and an inert oxygen atom. By these data and the fission products of the above mentioned alkaline degradation, the presence of a 2-methyl-γ-pyrone ring in rubrofusarin (ν_{max}^{KBr} 1660 cm^{-1}) is indicated. It is further supported by the following reactions of rubrofusarin dimethyl ether; the ether gave a violet colour reaction with m-dinitrobenzene at the presence of alkali and condensed with piperonal to give a styryl compound, yellow needles, m.p. 254.5°.

From the above results, rubrofusarin is assigned the 2-methylnaphthopyrone structure (II or III) instead of the so far proposed xanthone structure (I). The position of the methoxy group is derived from the fact that acetylation of a alkaline degradate of rubrofusarin gave a methoxytriacetoxynaphthalene (IVd), m.p. 128°, showing a β-naphthol type ul-

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[10] Garden and Thompson reported that the fusion results in the formation of 2,4-dihydroxybenzoic acid. We have succeeded this attempt by carrying out the fusion using an alkali mixture ($Ba(OH)_2.8H_2O$, KOH and NaOH) in an atomosphere of nitrogen at 260° (oil bath) for 7 hrs. in 10% yield (as the tetraacetate).
J.F.Garden and R.H.Thompson, J. Chem. Soc. 2483 (1957).

traviolet spectrum. λ_{max} 235, 282, 317, 331 mμ (log ε 4.80, 3.69, 3.19, 3.24 resp.), λ_{min} 256, 312, 324 mμ (log ε 3.44, 3.15, 3.12 resp.). Both the structures II and III are in well accord with the acetate theory and with the statement of Lund et al.[3] that nor-rubrofusarin has a hydroxyl group in o-position to a carbonyl group. The ultraviolet spectrum of nor-rubrofusarin triacetate favours the structure II. Since a Wessely-Moser rearrangement between the structure II and III is expected, rubrofusarin should be examined for this isomeric change.

The details of this work and of further studies which are in progress will be found in the Bulletin of the Agricultural Chemical Society of Japan.

All melting points are uncorrected. Ultraviolet spectra were determined for 95% ethanol solutions on a Hitachi EPS-2 recording spectrophotometer.

Our sincere thanks are due to Dr. K. Munakata, Messrs. H. Aoki and S. Kuyama for helpful advices, and to the late Miss M. Miyata for the microanalysis.

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CYCLOPROPANKOHLENWASSERSTOFFE AUS ALLYLHALOGENIDEN

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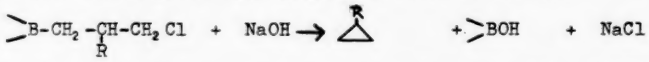
Max-Planck-Institut für Kohlenforschung, Mülheim-Ruhr

(Received 16 January 1961; in revised form 17 February 1961)

1961

DIE zuerst von L.H.Sommer, R.E.van Strien und F.C. Whitmore[1] beschriebene Synthese von Cyclopropankohlenwasserstoffen aus 3-Halogenalkylsilanen wurde von M.F.Hawthorne[2] auf die entsprechenden organischen Borverbindungen ausgedehnt. Danach reagieren die aus Diboran und Allylhalogeniden dargestellten 3-Halogenalkylborane mit wässrigem Natriumhydroxyd unter Bildung von Cyclopropankohlenwasserstoffen.



Diese Arbeitsweise besitzt gegenüber den im folgenden beschriebenen Ausführungsformen einige Nachteile. Es stellte sich heraus, daß die Cyclopropankohlenwasserstoff-synthese immer dann zu besseren Ergebnissen (hohe Ausbeuten, kleinste Verluste an borhaltigen Verbindungen) führt, wenn man die Spaltung der 3-Halogenalkylborane im nichtwässrigen Medium durchführt. Auch ist die Verwendung von Alkyldiboranen (insbesondere Tetraalkyldiboranen) für die Darstellung der 3-Halogenalkylborane günstiger als der Einsatz von Diboran.

Wir fanden, daß 3-Halogenalkylborane (z.B. $R_2B\text{-}CH_2\text{-}CH_2\text{-}CH_2X$) auch durch Alkalihydride bzw. Alkalialkyle unter Bildung von Cyclopropankohlenwasserstoffen gespalten werden.

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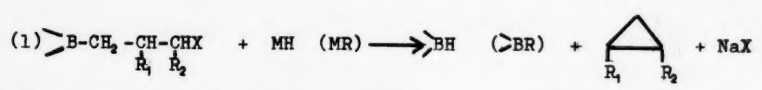
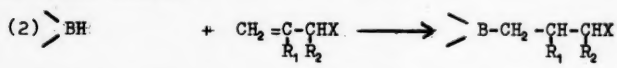
[1] L.H.Sommer, R.E.van Strien und F.C.Whitmore, J.Amer.Chem.Soc. 71, 3056 (1949).

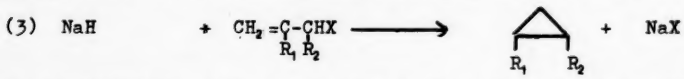
[2] M.F.Hawthorne, J.A.Dupont, J.Amer.Chem.Soc. 80, 5830 (1958).
M.F.Hawthorne, J.Amer.Chem.Soc. 82, 1886 (1960).

(1) 

Bei Verwendung der Metallhydride werden gleichzeitig Alkyldiborane gebildet, die sich mit Allylhalogeniden in die 3-Halogenalkylborane umwandeln lassen[3].

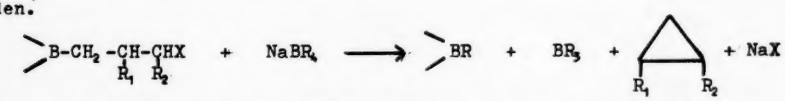
(2) 

Durch Kombination der Gleichungen (1) und (2) ergibt sich somit eine Darstellungsmethode für Cyclopropankohlenwasserstoffe nach der unmittelbar nicht zu verwirklichenden Bruttogleichung (3). z.B.

(3) 

Die Alkalihydride werden am besten in Form ihrer Komplexverbindungen mit Trialkylboranen BR_3 bzw. RB<R' oder auch mit Borsäureestern verwendet, da man dann in Kohlenwasserstoffen als Lösungsmitteln arbeiten kann. Die Ausbeuten an Dreiringverbindungen sind dann praktisch quantitativ.

Entsprechend verlaufen die Reaktionen in Gegenwart von Alkalialkylen, die vorteilhaft in Form der Alkalibortetraalkyle MBR_4 eingesetzt werden.[4]



In hohen Ausbeuten (vgl. Beispiel) entstehen neben den Dreiringver-

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[3] P.Binger, Dissertation Techn.Hochschule Aachen (1960)

[4] M.F.Hawthorne hatte bei der Einwirkung von Phenyllithium auf 3-Chlorpropylboran in 84%iger Ausbeute Cyclopropan erhalten (vgl.[2]).

bindungen Trialkylborane, die leicht wieder in Alkyldiborane bzw. Alkalibortetraalkyle umgewandelt werden können.

Beispiel (Methylcyclopropan).- In eine auf 120-130°C erhitzte Lösung von 20.6 g (0.1 Mol) Natriumbortetrapropyl (Schmp.= 148°C) in 80 ccm absol. Xylol werden unter Rühren langsam 18.8 g (0.1 Mol) Propyl-(3-chlor-2-methylpropyl)boran - dargestellt aus 9.8 g (0.05 Mol) Tetrapropyldiboran und 9.0 g (0.1 Mol) Methallylchlorid - eingetropft. Methylcyclopropan entweicht sofort, Natriumchlorid fällt aus. Nach etwa 45 min ist die Reaktion beendet. Man erhält 5.4 g (96.5 % d.Th.) Methylcyclopropan in 98%iger Reinheit (Rest Propen). Nach Abfiltrieren vom NaCl (5.5 g) werden aus dem Filtrat (nach Abdestillieren des Lösungsmittels) 26.5 g (94.6 % d.Th.) Tripropylboran gewonnen.

Folgende Cyclopropankohlenwasserstoffe wurde so dargestellt:

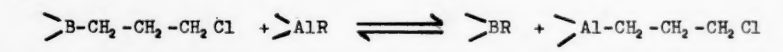
Allylhalogenid	Cyclopropan-KW	Ausbeute (%)
3-Chlorpropen-(1)	Cyclopropan	00
3-Chlor-2-methylpropen-(1)	Methylcyclopropan	96.5
2-Chlormethylpenten-(1)[5]	n-Propylcyclopropan	88
3-Chlor-2-methylpenten-(1)[5]	trans- und cis-Methyl-äthylcyclopropan im Molverhältnis 1:1	86
3-Brompropen-(1)	Cyclopropan	69

Auch Alkalialuminiumtrialkylhydride $M(AlR_3H)$ bzw. Alkalialuminiumtetraalkyle $MAlR_4$ reagieren mit 3-Chloralkylboranen glatt unter Bildung von

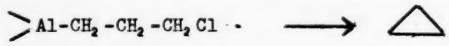
[5] Diese Verbindungen stellte uns W.Haaf (Mülheim-Ruhr) freundlicher Weise zur Verfügung.

Cyclopropankohlenwasserstoffen. z.B.

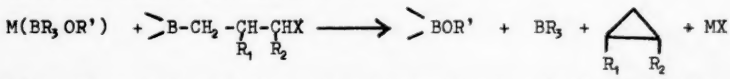
Auf dieser Stufe bleibt die Reaktion jedoch nicht stehen, da Aluminiumtrialkyle AlR_3 bzw. Dialkylaluminiumhydride R_2AlH mit 3-Halogenalkylboranen ihre Alkylgruppen bereits bei tiefer Temperatur rasch austauschen.[6] z.B.



3-Halogenalkylaluminium-verbindungen zerfallen aber bereits unterhalb Raumtemperatur unter Cyclopropan-bildung gemäß folgender Gleichung.



Außer den Alkalihydriden und -alkylen sind auch Alkalialkoholate bzw. deren Komplexverbindungen mit Trialkylboranen $M(BR_3OR')$ für die Abspaltung von Cyclopropankohlenwasserstoffen aus 3-Halogenalkylboranen in wasserfreiem Medium geeignet. z.B.



Die Wiedergewinnung der hierbei entstehenden bororganischen Verbindungen (Alkylborsäureester) ist jedoch mit gewissen Schwierigkeiten verbunden, weshalb die Spaltungen mit den Hydriden und Alkylen vorzuziehen sind.

Die Darstellung von Cyclobutan-kohlenwasserstoffen aus 4-Halogenalkylboranen gelingt nicht.[2] Tri-(4-chlorbutyl)boran ist beispielsweise eine ohne Borchlorid-bildung destillierbare Flüssigkeit ($Sdp._{10^{-5}}$ = 126-8°C). Im Gegensatz hierzu zerfallen aber 4-Chlorbutylaluminiumdialkyle (z.B. $(C_2H_5)_2Al(CH_2)_4Cl$) bereits ab etwa 6o°C in Dialkylaluminiumchlorid und

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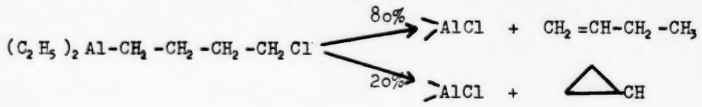
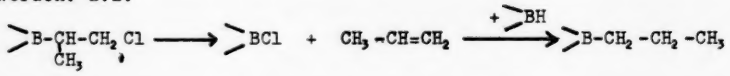
[6] R.Köster und G.Bruno, Liebigs Ann.Chem. 629, 89 (196o).

ein Gemisch aus Buten-(1) und Methylcyclopropan. z.B.

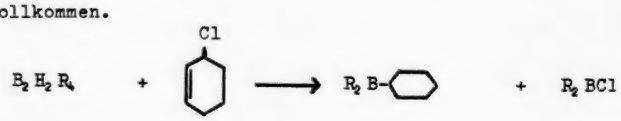


Bei der Hydroborierung von Allylhalogeniden werden neben den 3-Halogenalkylboranen auch 2-Halogenalkylborane gebildet, die für die Cyclopropan-synthese nicht geeignet sind. Vielmehr sind 2-Halogenalkylborane instabil und zerfallen bereits bei Raumtemperatur in Borhalogenide und Olefine, die dann an noch vorhandene BH-bindungen addiert werden. z.B.



Während jedoch zwischen Diboran B_2H_6 und Allylchlorid diese unerwünschte Nebenreaktion zu mehr als 3o% verläuft, tritt sie bei Verwendung von Tetraalkyldiboranen (z B. Tetraäthyldiboran) nur zu etwa 1o % ein, weshalb die Ausbeuten an Cyclopropan-kohlenwasserstoffen entsprechend höher liegen. Schließlich gibt es auch Allylhalogenide (z.B. 3-Chlorcyclohexen-(1)), die ausschließlich in 2-Stellung halogenierte Alkylborane bilden. Bei derartigen Verbindungen versagt demnach die Darstellung der Cyclopropan-Kohlenwasserstoffe nach der angegebenen Methode vollkommen.

z.B.



Tetrahedron Letters No.5, pp.161-166, 1961. Pergamon Press, Inc. Printed in the United States of America.

PHOSPHORORGANISCHE VERBINDUNGEN[1]

OPTISCH AKTIVE TERTIÄRE PHOSPHINE AUS OPTISCH AKTIVEN QUARTÄREN PHOSPHONIUMSALZEN

L. Horner, H. Winkler, A. Rapp, A. Mentrup,
H. Hoffmann und P. Beck
Aus dem Institut für organische Chemie der Universität Mainz

(Received 22 February 1961)

QUARTÄRE Phosphoniumsalze mit geeigneten Substituenten können kathodisch schnell und in hohen Ausbeuten zu tertiären Phosphinen abgebaut werden. Struktur, Siedepunkte und Ausbeuten einiger unsymmetrisch substituierter tertiärer Phosphine P R_1 R_2 R_3 sind Tabelle 1 zu entnehmen.

Durch Einbau eines 4. von den 3 übrigen strukturell verschiedenen Liganden sind asymmetrisch substituierte quartäre Phosphoniumsalze leicht zugänglich. Es wurden bisher folgende quartäre Phosphoniumsalze $P(CH_3)(C_6H_5)(CH_2C_6H_5)R$ Br dargestellt:

R: Äthyl (145°)*; n-Propyl (185°); Allyl (142°); tert. Butyl (149°); Benzhydryl (100-120° u.Z.); p-Nitrobenzyl (174°); CH_2-CO_2H (163°); CH_2-$CO_2C_2H_5$ (153°); CH_2-COC_6H_5 (171°); CH_2-CO_2bornyl (180°); CH_2-CO_2menthyl (177°); 4-Phenoxybutyl (112°); $P(C_2H_5)(C_6H_5)(CH_2C_6H_5)(CH_2$-$CH=CH_2)$ Br (154°).

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[1] XXIX.Mitteil.: Chem.Ber. z.Zt. im Druck

* bedeutet jeweils Schmelzpunkt

Tabelle 1:

	R_1	R_2	R_3	Sdp. (°C)	Ausbeute (%)
1.	Methyl	Äthyl	Phenyl	96-97 15 Torr	77
2.	Äthyl	Allyl	Phenyl	113-115 15 Torr	71
3.	Äthyl	n-Butyl	Benzyl	137-139 16 Torr	86
4.	Äthyl	n-Butyl	Dodecyl	188-191 13 Torr	83
5.	Methyl	Phenyl	Benzyl	156-158 12 Torr	86
6.	Äthyl	Phenyl	Benzyl	168 12 Torr	91
7.	n-Propyl	Phenyl	Benzyl	173-174 12 Torr	82
8.*	Methyl	Phenyl	p-Methoxy-phenyl	153-156 0,8 Torr	65
9.	Methyl	Phenyl	Methyl-dimethylen-phenyl-phosphin	-	82
10.	Methyl	Phenyl	Methyl-tetramethy-len-phenyl-phosphin	178-180 1 Torr	80

* Aus dem Phosphinoxyd mit $LiAlH_4$.

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Vander Werf und Mitarbeiter[2] konnten 1959 Methyl-äthyl-benzyl-phenylphosphoniumsalz als ersten Vertreter eines nicht cyclischen quartären Phosphoniumsalzes[3] über das saure (D-) Dibenzoyltartrat in optische Antipoden spalten. Sie überführen das Jodid (Schmp. 160°, $[\alpha]_D^{25} = +24^\circ$) mit Alkali unter Inversion in das optisch aktive Methyl-äthyl-phenylphosphinoxyd ($[\alpha]_D^{25} = -22{,}8^\circ$)[4]; den Antipoden ($[\alpha]_D^{25} = +22{,}4^\circ$) erhielten sie als Ergebnis einer Wittig-olefinierung[5]. Die Konfiguration bleibt bei dieser Umsetzung erhalten.

Wir haben mit verbesserter Methodik Methyl-n-propyl-phenyl-benzylphosphonium-bromid (I), Methyl-allyl-phenyl-benzylphosphonium-bromid (II) sowie Methyl-äthyl-benzyl-phenylphosphonium-bromid dargestellt, mit saurem Silber-(D-) Dibenzoyltartrat in die Antipoden gespalten und anschließend kathodisch reduziert. Unter Abspaltung der Benzylgruppe als Toluol erhält man die optisch aktiven tertiären Phosphine IV, V, VI. Die Tabellen 2 und 3 enthalten die bisher gefundenen Daten.

Die Verbindung IV racemisiert in siedendem Toluol auch nach 3 Stunden nur unwesentlich. Sie kann bei 86-88°, 2,5-3 Torr mit nur geringem Drehungsverlust ($[\alpha]_D = +36{,}8 \rightarrow +29{,}1^\circ$)

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[2] K.F. Kumli, W.E. McEwen, C.A. Vander Werf, J.Amer.chem.Soc. 81, 248 (1959)

[3] F.A. Hart u. F.G. Mann, J.chem.Soc. 4107 (1955)

[4] K.F. Kumli, W.E. McEwen, C.A. Vander Werf, J.Amer.chem.Soc. 81, 3805 (1959)

[5] A. Bladé-Font, C.A. Vander Werf, W. McEwen, J.Amer.chem.Soc. 82, 2396 (1960)

destilliert werden, wird jedoch bei der Destillation unter Normaldruck (ca. 230°) inaktiv. Die Verbindung V racemisiert leichter. Es spielt sich vielleicht im Sinne einer Allylumlagerung ein innermolekularer Platzwechsel ab.

Bei der Alkylierung, Oxydation und Behandlung mit Schwefel bleibt die Konfiguration erhalten. Damit ergibt sich ein neuer und präparativ leistungsfähiger Weg zur Darstellung neuer, optisch aktiver quartärer Phosphoniumsalze, Phosphinoxyde und Phosphinsulfide. Die beiden enantiomorphen Formen des Methyl-n-propyl-phenylphosphinoxyds lassen sich z.B. gewinnen:

a) durch Spaltung von I mit Alkalien (Inversion) und

b) durch Oxydation von IV mit Wasserstoffperoxyd.

IV gibt mit Äthyljodid aktives Methyl-äthyl-n-propyl-phenylphosphonium-jodid (Schmp. 62°; $[\alpha]_D$ = 4,6°, C = 1,732 in Methanol); mit Methylbromid erhält man erwartungsgemäß das optisch inaktive Dimethyl-n-propyl-phenyl-phosphoniumbromid (Schmp. und Mischschmp. 118°). Die vorliegende Untersuchung beweist endgültig, daß der Phosphor in den tertiären Phosphinen an der Spitze einer trigonalen Pyramide steht und im Gegensatz zum Stickstoff nicht durch die Ligandenebene hindurchschwingt. Dieser Befund erklärt eine Reihe auffälliger Unterschiede zwischen tertiären Aminen und tertiären Phosphinen, z.B. das hohe Dipolmoment und das ausgeprägte nukleophile Verhalten der tertiären Phosphine[6].

---

[6] L. Horner und K. Klüpfel, Liebigs Ann.Chem. 591, 69 (1955); H. Hoffmann, Chem.Ber. z.Zt. im Druck

Tabelle 2:

Optisch aktives Phosphoniumsalz	Schmp. (°C)	$[\alpha]_D$
I	201	+ 36,8 ± 1 C = 1,507 (Methanol)
II	126-127	+ 15,7 ± 1 C = 1,908 (Methanol)
III	144	+ 21 ± 2 C = 0,82 (Methanol)

Tabelle 3:

Optisch aktives tert. Phosphin	$[\alpha]_D$	Sdp. (°C)	n_D	$[\alpha]_D$ nach Rückbenzylierung
IV	+ 16,8 C = 5,170 (Toluol) + 14,9 C = 1,823 (Methanol)	86-88 3 Torr	1,5451	+ 34,9 C = 1,952 (Methanol)
V	ca. $-10^{\circ} \pm 1^{\circ}$ C = 4,5±0,5 (Toluol)	-	-	ca. + 9° C = 1,81 (Methanol)
VI	+ 1,5 ± 0,5 C = 6± 2 (Toluol)	-	-	+ 19,5± 2 C = 0,82 (Methanol)

C = g/100 ccm Lösungsmittel

Die Versuche werden in den verschiedensten Richtungen fortgesetzt.

Wir danken der Deutschen Forschungsgemeinschaft, dem Verband der Chemischen Industrie und den Farbwerken Hoechst für die gewährte Unterstützung.

Tetrahedron Letters No.5, pp.167-172, 1961. Pergamon Press, Inc. Printed in the United States of America.

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ALLENES FROM gem-DIHALOCYCLOPROPANE DERIVATIVES AND ALKYLLITHIUM

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Belgium

(Received 8 February 1961)

IN a recent communication [1] Moore and Ward describe the preparation of allenes from gem-dibromocyclopropanes and alkyllithium. We wish to report some additional results, particularly the preparation of two cyclic diallenes, which further establish the generality of this reaction.

gem-Dibromocyclopropanes gave allenes in good yields when treated with methyl- or buthyllithium in ether. The dichloro analogues also reacted readily with butyl-lithium, but we have not been able to observe any reaction with methyllithium. Table I gives some of the results obtained.

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[1] W.R. Moore and H.R. Ward, J. Org. Chem. 25, 2073 (1960).

TABLE I

The reaction between 1,1-dihalocyclopropanes and alkyllithium.

gem-Dibromocyclopropane derivative of	alkyl-lithium	allene	yield %
Trimethylethylene	MeLi	2-methylpenta-2,3 diene	69 [a]
"	BuLi		68
Tetramethylethylene	MeLi	2,4-dimethyl-penta-2,3-diene	73 [a]
"	BuLi	"	69
Hexa-1,5-diene	MeLi	hepta-1,2,6-triene	72 [b]
1,1-Diphenylethylene	MeLi	1,1-diphenylpropa-1,2-diene	43 [c]
Styrene	MeLi	1-phenylpropa-1,2 diene	82 [a]
Cyclooctene	MeLi	cyclonona-1,2-diene	93 [d]
Cycloocta-1,5-diene	MeLi	cyclonona-1,2,6-triene	76 [e]

[a] b.p. and refractive index were identical with those of the literature. [b] b.p. 102°, n_D^{24} 1.4551, (Found:C, 88.93 ; H, 10.78 %). [c] b.p. 75-76°/0.01 mm, n_D^{20} 1.6313 (Found : C, 92.88 ; H, 6.23 %). The compound polymerized during the distillation. [d] b.p. 62°/16 mm, n_D^{20} 1.5060 (Found : C, 88.43 ; H, 11.44 %). [e] b.p. 61°/13 mm, n_D^{24} 1.5216 (Found : C, 89.60 ; H, 9.84 %).

All the gem-dihalo cyclopropane derivatives were prepared from the olefins and dibromocarbene essentially as described by Doering and Hoffmann. [2] The halide was dissolved in dry ether, and the ethereal alkyllithium was added dropwise with stirring usually at -30 to -40°. The allenes were characterized by their boiling points, refractive indices and analyses. The infrared spectra supported the identity of

[2] W. von E. Doering and A.K. Hoffmann, J. Am. Chem. Soc. 76, 6162 (1954).

the products and further showed to what extent an allene-acetylene rearrangement had taken place. This was rare when methyllithium was used ; with butyllithium, however, a certain amount of rearrangement occurred probably because of the unavoidable presence of alkoxides in this reagent. Another disadvantage encountered using butyllithium was the separation of the allenic product from the butyl halide formed in the reaction. Thus, 1, 1-dichloro-2,2,3- trimethyl-cyclopropane with butyllithium yielded 2-methylpenta-2, 3-diene, as indicated by the infrared spectrum, but a separation from butyl chloride was not achieved. Generally the best results were obtained using the gem-dibromocyclopropanes and methyllithium.

Cycloocta-1,5-diene gave with dibromo-carbene besides the monoadduct also 34% of 9,9,10,10-tetrabromotricyclo [7,1,0,$0^{1,8}$] decane (I), m.p. 174-180° (Found : C, 26.69 ; H, 2.62 %). In the same way cyclotetradeca-1,9-diene gave 22% of 15, 15, 16, 16-tetrabromotricyclo [13, 1, 0, $0^{1,14}$] hexadecane (II), m.p. 200-204° (Found : C, 35.68 ; H, 4.38 %). When (I) was treated with methyl-lithium at -40° a small amount of cyclodeca- 1,2,6,7-tetraene (III) was obtained, m.p. 36° (Found : C, 90.74 ; H, 9.31 %). The infrared spectrum shows strong bands at 1960 and 856 cm^{-1} characteristic of the allene grouping. [3] No acetylenic absorption was

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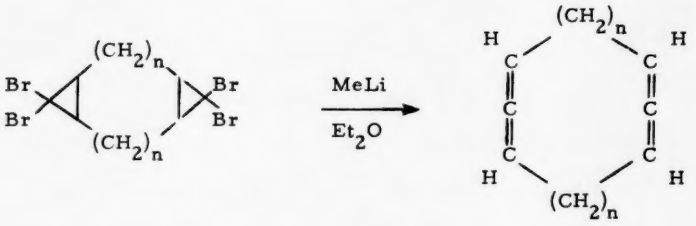
[3] J.H. Wotiz and D.E. Mancuso, J. Org. Chem. 22. 207 (1957).

present. The ultraviolet spectrum shows only end-absorption down to 200 mμ. Similarly (II) yielded 52 % of cyclohexadeca-1,2,9,10-tetraene (IV), m.p. 80° (Found : C, 88.75 ; H, 11.13 %). The infrared spectrum shows strong bands at 1970 and 894 cm^{-1} and no acetylenic absorption. In the ultraviolet region only end-absorption is observed. The structure of these cyclic diallenes was further established by ozonolysis and subsequent oxidation by peracetic acid [4] to the expected dicarboxylic acids.



I (n = 2)

II (n = 5)

III (n = 2)

IV (n = 5)

We have not been able to obtain any allenic products from the reactions of 7,7-dibromobicyclo[4,1,0] heptane or 8,8-dibromobicyclo[5,1,0] octane with methyllithium at -70°. In the former case the main products were a low boiling olefin and a high boiling oxygen-containing liquid.

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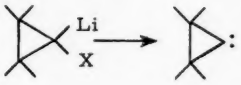
[4] Wilms, Ann. 567, 96 (1950).

From the residue a small amount of a crystalline compound was obtained which after recrystallization and sublimation melted at 124°C (Found : C, 89.17 ; H, 10.73 % ; mol. wt. [5] 188), U.V. λ_{max} (n-hexane ; 1 mm cell) 198 mμ (ε ~ 15000) and 206 mμ (shoulder ; ε ~ 13500). The infrared spectrum (KBr disc) has a band at 2985 cm^{-1} [6], and no bands indicating olefinic bonds. The N.M.R. spectrum [7] at 60 M.C. in deuterated benzene shows three bands at τ = 8.20, 8.30 & 8.68 relative to tetramethylsilane as internal standard and the absence of olefinic protons. There is little doubt that this compound is identical with that, m.p. 120.5 - 121°C, isolated by Moore and Ward [1], who assigned the structure (V).

V



(X = Cl or Br) VI

An attempt to demonstrate the existence of the carbene intermediate (VI), suggested [8] for a related reaction, by using any of the gem-dihalocyclopropane derivatives and isobutylene, tetramethylethylene or triphenylphosphine as acceptors failed.

Miller and Kim [9] have generated dihalocarbenes by treatment

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[5] We thank Dr. J. Block for the mass-spectrometric determination.

[6] This could be the cyclopropane C-H stretching vibration.

[7] Kindly carried out by Dr. J.F.M. Oth.

[8] W. von E. Doering and P.M. La Flamme, Tetrahedron 2, 75 (1958).

[9] W.T. Miller and C.S.Y. Kim, J. Am. Chem. Soc. 81, 5008 (1959).

of carbon tetrahalides with alkyllithium. When we reacted an equimolar mixture of carbon tetrabromide and trimethylethylene with an excess of methyllithium (> 2 moles per mole CBr_4), 50 % yield of 2-methylpenta-2,3-diene was obtained. This result may also explain the low yield of dibromonorcarane (11 %) obtained by the above authors from a reaction of carbon tetrabromide and butyllithium in the presence of cyclohexene.

Acknowledgement is due to Mr. I. Litvin and Mr. G.G.P. Vrambout for technical assistance. This work was supported by Union Carbide Corporation, New York, N.Y.

I am indebted to the directors of this institute, Dr. R.H. Gillette and Dr. C.E. Sunderlin for their interest in this work.

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CONVERSION OF 1,1-DICHLORO-2-ALKYLCYCLOPROPANES TO ALLENES AND CYCLOPROPANES

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(Received 2 March 1961)

We wish to report the reaction of 1,1-dichloro-2-alkylcyclopropanes with Mg metal and alkyl or aryl halides to yield 1,2-alkadienes (allenes) and alkylcyclopropanes as the principal products. To our knowledge, this is the first reported preparation of allenes from the dichlorocarbene ($:CCl_2$) adducts of olefins.

Doering and La Flamme have reported[1,2] that the dibromocarbene adducts of some olefins, such as 1-pentene, react readily with active metals (e.g. Na or Mg) to yield allenes, but that the corresponding dichloro compounds do not react under similar or more vigorous conditions. Moore and Ward have recently reported[3] that allenes are produced in high yields by the

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1 Wm. von E. Doering and P. M. La Flamme, Tetrahedron 2, 75 (1958).

2 Wm. von E. Doering and P. M. La Flamme, "Process for Increasing the Carbon Chain Length of an Olefin," U.S. Patent 2,933,544, April 19, 1960.

3 W. R. Moore and H. R. Ward, J. Org. Chem. 25, 2073 (1960).

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reaction of 1,1-dibromocyclopropanes with n-butyllithium. The reaction reported herein differs from the Moore reaction since we have found that n-butyllithium reacts with the corresponding dichloro compounds to give only a small yield of allene, accompanied by a multiplicity of other products. In addition, cyclopropanes are not formed in the Moore reaction.

In a typical example, 1,1-dichloro-2-decylcyclopropane, 6.3 g (0.025 mole), Mg shavings, 12.15 g (0.5 mole), and 200 ml of anhydrous ether were placed in a 500 ml, 3-necked flask equipped with stirrer, reflux condenser, and dropping funnel. Over a period of 1 hr, 54.5 g (0.5 mole) of ethyl bromide was added at a rate sufficient to maintain reflux. When the addition was completed, the contents were refluxed an additional hour, then carefully hydrolyzed by the dropwise addition of water, followed by 10% HCl. The ether layer was separated, dried, and distilled to give 2.6 g of liquid, b.p. 68-94° (0.85 mm), and 1.2 g of high boiling hydrocarbon residue. By gas chromatographic analysis, the distillate consisted of 44% decyl allene, 33% decylcyclopropane, 5% starting material, and 18% of unidentified minor components (assuming that peak area percentages are equal to weight percentages). By gas chromatographic comparison with known samples of 1- and 2-tridecyne, it was shown that neither of these products was present in the distillate. Infrared analysis also showed the absence of the 1-alkyne.

The two major components were separated by preparative-scale gas chromatography[4] for identification. Decylcyclopropane was identified by

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[4] We are indebted to Dr. C. H. Orr for this separation.

comparing an infrared spectrum and a gas chromatogram of an authentic sample (prepared by the Na-MeOH reduction[5] of 1,1-dibromo-2-decylcyclopropane) with those of the product. Decyl allene was identified by the strong infrared absorption at 5.1 μ and by hydration[6] to 2-tridecanone. The 2,4-dinitrophenylhydrazone derivative m.p. and mixture m.p. with an authentic sample was 71.8-72.0°.

Other halides which have been successfully employed in this reaction are methyl iodide, ethyl iodide, ethyl chloride, t-butyl chloride, bromobenzene, and p-bromoanisole. Dichlorocarbene adducts of 1-octene and 1-octadecene were also prepared and reacted with alkyl halides and Mg as above to give the corresponding allenes and cyclopropanes. In all examples studied thus far, the allene and cyclopropane are the major products and no evidence for acetylene formation has been observed.

The reaction of dibromo compounds with Mg, which was described by Doering[1], resembles the reaction of dichloro compounds with Mg and alkyl or aryl halides reported herein, since both reactions yield allene-cyclopropane mixtures. Although Doering reported that the other products of his reaction apparently were isomeric acetylenes, formed by an active metal-catalyzed allene-acetylene interconversion, we have now demonstrated that the alkylcyclopropane is the other major product from the reaction of either 1,1-dibromo-2-propylcyclopropane or 1,1-dibromo-2-hexylcyclopropane with Mg metal.

Attempts to trap a possible carbene intermediate with cyclohexene have thus far proven unsuccessful. Further work on the mechanism of this reaction is in progress and will be reported at a later date.

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5 Wm. von E. Doering and A. K. Hoffmann, J. Am. Chem. Soc. 76, 6162 (1954).

6 G. F. Hennion and J. J. Sheehan, ibid. 71, 1964 (1949).

Tetrahedron Letters No.5, pp. 176-182, 1961. Pergamon Press, Inc. Printed in the United States of America.

THE STRUCTURE OF SWERTIAMARIN

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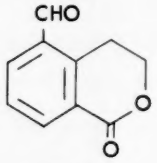
(Received 10 February 1961)

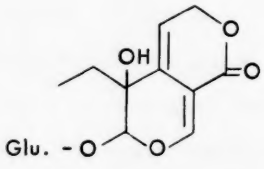
SWERTIAMARIN (I), a bitter principle of Swertia Japonica Makino, affords erythrocentaurin (II) and glucose by the enzymatic hydrolysis with emulsin as follows:[1,2,3]

$$\underset{\text{I}}{C_{16}H_{22}O_{10}} + H_2O \longrightarrow \underset{\text{II}}{C_{10}H_8O_3} + C_6H_{12}O_6 + 2H_2O$$

We have proposed formula II for erythrocentaurin[3] and recently confirmed its structure by synthesis.[4] Although formula IA has also been proposed for swertiamarin in our previous report,[5] we now wish to propose structure IB for this substance on the basis of subsequent, experimental evidence.



II



IA

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[1] T. Kariyone et al. J.Pharm.Soc.Japan 47, 133 (1927); 49, 702 (1929).

[2] T. Kubota and Y. Tomita, Chem. & Ind. 1958, 229.

[3] T. Kubota and Y. Tomita, ibid. 1958, 230.

[4] T. Kubota and Y. Tomita, Tetrahedron Letters to be submitted.

[5] Y. Tomita and T. Kubota, 'Abstracts of Papers of the 2nd Symposium on Natural Products, Japan', p. 17 (1958).

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1) Swertiamarin acetate (III), $C_{24}H_{30}O_{14}$, m.p. 190-191°, rapidly decolorized aqueous permanganate solution, slowly consumed bromine in acetic acid solution, gave a negative color reaction with tetranitromethane, and showed a red color with triphenyltetrazolium chloride. Infrared spectrum showed the presence of hydroxyl group (2.85 μ) resisting to acetylation, conjugated double bond (6.18 μ), α,β-unsaturated-δ-lactone (5.89 μ), and trisubstituted double bond (11.9 μ). Ultraviolet spectrum showed two absorption maxima at 206 mμ (log ε 3.2) and 234 mμ (log ε 4.0).

2) When swertiamarin acetate (III) was hydrogenated in the presence of platinum catalyst in acetic acid, dihydroswertiamarin acetate (IV), $C_{24}H_{32}O_{14}$, m.p. 175-176°, with a single maximum at 233.5 mμ (log ε 4.0), was easily formed. Dihydroswertiamarin acetate showed infrared bands at 2.85, 5.89, 6.18, and 11.9 μ. On further hydrogenation IV slowly absorbed one mole of hydrogen to give tetrahydroswertiamarin acetate (V) as a liquid, whose infrared spectrum showed no bands at 5.88, 6.18, and 11.9 μ.

3) III and IV showed the presence of four acetoxy groups in the molecules by hydrolysis with sulfuric acid or with p-toluenesulfonic acid followed by titration of the resulting volatile acid with alkali. When III and IV were hydrolyzed with an excess of 0.1 N potassium hydroxide for twenty four hours at room temperature, five moles of alkali were consumed. On vigorous hydrolysis (two hours' refluxing with 0.1 N potassium hydroxide) III consumed six moles of alkali. When this hydrolysate was acidified with sulfuric acid followed by steam distillation, the distillate consumed five moles of alkali and formic acid was detected in the distillate.

4) The Kuhn-Roth determination showed the presence of four C-methyl groups in III and five C-methyl groups in IV. While the ozonization of III gave formaldehyde together with formic acid and carbon dioxide, the ozonization of IV merely gave formic acid and carbon dioxide. When IV was hydrolyzed with dilute hydrochloric acid followed by chromium trioxide oxidation of the resulting liquid, one mole equivalent of a mixture of volatile fatty acids was obtained, from which acetic acid and propionic acid were detected (paper chromatography and p-bromophenacyl esters).

IV had no infrared bands at 3.25, 9.93, and 10.66 μ, which were originally present in the infrared spectrum of III. These evidences suggests that swertiamarin has CH_2=CH- group.

5) The ultraviolet absorption maximum (233.5-234 mμ) of III and IV shows too great a bathochromic shift to be considered as α,β-unsaturated-δ-lactone with trisubstituted double bond, and in the infrared spectrum, the intensity of the band at 6.18 μ is anomalously strong. These phenomena can be explained by considering that the carbon atom in the α- or β-position of the unsaturated lactone group is attached to an oxygen linkage.[6,7] Furthermore, the anomalous infrared band (5.89 μ) of the α,β-unsaturated-δ-lactone of III and IV is in agreement with the known bathochromic shift which occurs by the appearance of an oxygen linkage in the β-position of an α,β-unsaturated ketone.[8] Since the oily products obtained from III and IV by acid hydrolysis gave a negative reaction with ferric chloride, we

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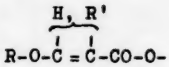
6 F. E. Bader, Helv.Chim.Acta 36, 216 (1953); H. Schmid et al, ibid. 41, 1109 (1958); F. Korte and K. H. Bückel, Chem.Ber. 92, 877 (1959).

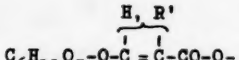
7 K. Nakanishi, 'Jikken-kagaku-koza' vol I, p. 336, Maruzen Co. (1957).

8 K. Nakanishi, Kagaku-no-ryoiki Extra edition vol. 21, 122 (1956).

can exclude the formula (B) from two possible partial formula, (A) and (B), for III and IV.

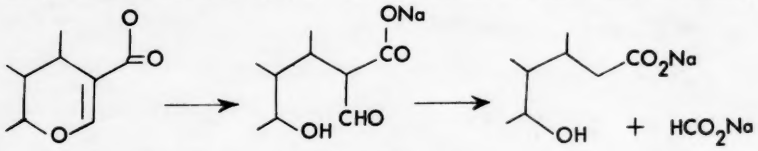


(A)

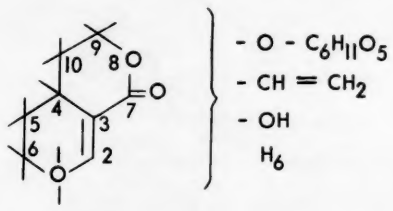


(B)

6) The empirical formula of swertiamarin suggests that the R-group in the formula (A) must incorporate a five or six-membered ring If we assume a dihydropyran ring as the R-group, the peculiarity of swertiamarin and its derivatives in their spectroscopic properties and their various reactions may be easily explained. For instance, the formation of formic acid by alkaline hydrolysis of swertiamarin acetate (cf. 3) can be showed as following sequence:



We can now show the partial structure IC for swertiamarin.



IC

7) The oily products obtained from III and IV by acid hydrolysis have no infrared bands (11.9μ corresponding to a trisubstituted double bond conjugated to the lactone group. The oily product obtained by acid hydrolysis of V gave a positive reaction with 2,4-dinitrophenylhydrazine. These facts show that the glucoside residue of swertia-

marin is bonded in the form of an acetal linkage. We assume that the glucoside linkage may be located at the C_6-position of two possible positions, C_2 and C_6, from analogy to aucubin and plumieride. Infrared bands at 10.8, 11.2, and 13.2 μ of swertiamarin show the presence of β-glucoside linkage.[9]

8) Swertiamarin acetate (III) was dehydrated with potassium hydrogen sulfate and acetic anhydride or with boron triflouride and acetic acid to give monoanhydroswertiamarin acetate (VI), $C_{24}H_{28}O_{13}$, m.p. 143-144°C, which had absorption maxima, 246 mμ (logε 3.44) and 269 mμ (logε 3.37). The latter maximum shows the presence of a conjugated triene in VI. This suggests that the tertiary hydroxyl group in III must be located at the α- or β-carbon atom of the vinyl group. The absorption maximum (243 mμ) of monoanhydrodihydroswertiamarin acetate, m.p. 161-162°C, which is obtained by dehydration of IV with potassium hydrogen sulfate and acetic anhydride, also suggests that the vinyl group is bonded to the carbon atom of the C_5- or C_{10}-position and the tertiary hydroxyl group is bonded to the carbon atom of the C_4-, C_5- or C_{10}- position. The formation of erythrocentaurin from swertiamarin, however, can more easily be explained as showed below, when the tertiary hydroxyl group is bonded to the C_4-carbon atom.

9) The above evidences show that swertiamarin has structure IB*, which may explain the mechanism of the formation of erythrocentaurin (II) as showed in the following sequence.

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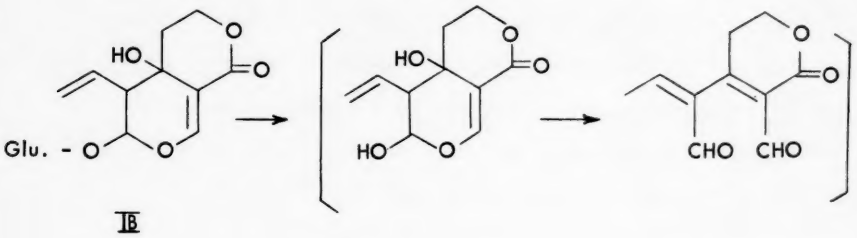
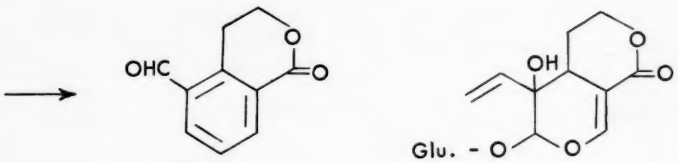
* Prof. G. Büchi has pointed out structure I as a possible structure of swertiamarin in his private communication which was sent us immediately after the preparation of this manuscript.

We, however, can not eliminate formula ID[10] for swertiamarin, since the negative color reaction of I and III with tetranitromethane may indicate an allylic structure of I.[12]



IB



II ID

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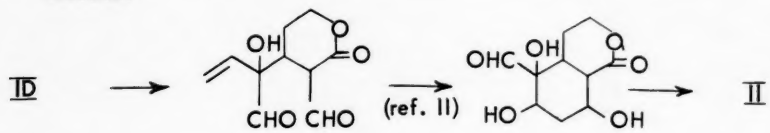
10 Formula ID may explain the formation of erythrocetaurin as follows:



ID II

11 Cf. E. Arnsdale, L. A. Mikesska, Chem.Rev. 51, 505 (1952).

12 E. Heilbronner, Helv.Chem.Acta 36, 1121 (1953).

10) Biogenetic considerations led us to the conclusion that swertiamarin may form through the precursor, from which gentianin is considered to be formed in plants of Gentianaceae.[13] We assume that erythrocentaurin is not formed through the above precursor but formed from swertiamarin by hydrolysis, although erythrocantaurin has been isolated from commercial samples of Erythrea centaullium.[14]

Acknowledgements - We wish to thank Professor G. Büchi for his valuable suggestion and also Professor D. H. R. Barton and Dr. T. Matsuura for kind discussions.

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[13] E. Wenkert, J.Am.Chem.Soc. 81, 1474 (1959).
[14] J. Mehu, Chem.Zent. 677 (1866), 877 (1870).

Tetrahedron Letters No.5, pp.183-186, 1961. Pergamon Press, Inc. Printed in the United States of America.

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STRUCTURE OF ESTRIOL GLUCURONIDE FROM HUMAN PREGNANCY URINE

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(Received 20 February 1961)

SODIUM estriol glucosiduronate was isolated from human pregnancy urine in 1936 by Cohen and Marrian,[2] but its complete structure remained unknown. We present evidence for the structure of pure estriol glucosiduronic acid isolated in our laboratory.

Twenty liters of third trimester human pregnancy urine was processed by a semi-continuous modification of the extraction sequence developed by Grant and Marrian.[3] However, the first extraction with n-butanol was done at pH 7.5, and the subsequent isolation proved to be more efficient. The

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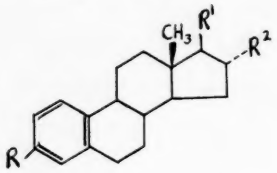
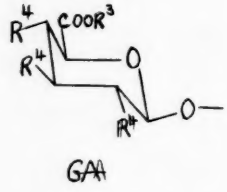
[1] Postdoctoral fellow supported by Institutional Grant to Roswell Park Memorial Institute from the United States Public Health Service.

[2] S.L. Cohen and G.F. Marrian, Biochem. J. 30, 57 (1936). In retrospect it seems probable that the isolated material may have been contaminated with glucuronides of 16-epiestriol, 16α-hydroxyestrone etc., though there is no evidence that this was actually the case (Dr. G.F. Marrian, private communication).

[3] J.K. Grant and G.F. Marrian, Biochem. J. 47, 1 (1950).

urine, in which 10-13 mg of estriol per liter was determined by analysis,[4] afforded 0.286g of crystalline sodium estriol glucosiduronate (I), m.p. 245° (dec.),[5] λ_{max}^{EtOH} 280mμ. Estriol glucosiduronic acid (II), previously described as amorphous,[3] was obtained crystalline for the first time by dissolving the salt I in water saturated with n-butanol and acidifying the solution with hydrochloric acid to pH 1. This procedure was repeated twice, affording analytically pure acid II as tiny white needles, 0.150g of II from 0.275g of I, m.p. 221-222° (dec.), λ_{max}^{EtOH} 280mμ (ε2100), $\lambda_{max}^{0.05N\ NaOH-EtOH}$ 300mμ (C, 61.79; H, 7.27; neutral equiv. 478).





GA

Compound	R	R^1	R^2	R^3	R^4
I	OH	OH	GA	Na	OH
II	OH	OH	GA	H	OH
III	OMe	OH	GA	Me	CH
IV	OMe	OMe	GA	Me	OMe
Va≡Vb	OMe	OMe	OH		
VI	OAc	=O	OAc		
VII	OAc	OH	OAc		
VIII	OAc	OMe	OAc		
IX	OH	OMe	OH		

Estriol glucosiduronic acid II, on treatment with diazomethane in dichloromethane - methanol, afforded the methyl ether-ester (III), λ_{max}^{EtOH} 278mμ, 286mμ. The ester III, without purification, was exhaustively

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[4] J.B. Brown, Biochem. J. 60, 185 (1955).

[5] All melting points were determined on a Kofler Audiohm Thermistor hot stage of A.H. Thomas Co., Philadelphia, Pa.

methylated by diazomethane in dichloromethane in the presence of boron trifluoride catalyst.[6] The totally methylated product (IV),[7] obtained in 49.5% overall yield from II, m.p. 140-141°, λ_{max}^{EtOH} 279mμ(ε1800), 287mμ (ε1620), $\lambda_{max}^{CH_2Cl_2}$ 5.72μ, 8.77μ(C, 65.78; H, 8.13), was hydrolyzed by boiling 4 N hydrochloric acid in 10% ethanol to 3,17β-dimethoxy-1,3,5(10)-estratrien-16α-ol (Va),[7] thin plates, m.p. 165-166°, λ_{max}^{EtOH} 279mμ(ε1990), 287mμ(ε1820). This degradation product Va had ultra-violet and infrared spectra superposable with those of the synthetic product Vb of unequivocal structure described below, and the compounds showed an undepressed mixture melting point.

The intermediate in the partial synthesis of estriol,[8] 3,16α-diacetoxy-1,3,5(10)-estratrien-17-one(VI), was reduced with sodium borohydride in methanol below +5° to 3,16α-diacetoxy-1,3,5(10)-estratrien-17β-ol (VII), m.p. 154.5-155.5°, λ_{max}^{EtOH} 268mμ(ε710), 275mμ(ε653), $\lambda_{max}^{CH_2Cl_2}$ 5.69μ, 5.79μ, 8.25μ(broad) (C, 71.12; H, 7.57; acetoxyl, 22.8).[9] Acid catalyzed diazomethane methylation[6] of VII afforded 3,16α-diacetoxy-17β-methoxy-1,3,5(10)-estratriene (VIII), m.p. 108-109°, λ_{max}^{EtOH} 268mμ(ε810), 275mμ(ε780),

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[6] M. Neeman, M.C. Caserio, J.D. Roberts and W.S. Johnson, Tetrahedron 6, 36 (1959).

[7] The compound was chromatographically pure.

[8] N.S. Leeds, D.K. Fukushima and T.F. Gallagher, J. Am. Chem. Soc. 76, 2943 (1954).

[9] A portion of VII was re-oxydized to VI by chromic anhydride-pyridine reagent, G.I. Poos, G.E. Arth, R.E. Beyler and L.H. Sarett, J. Am. Chem. Soc. 75, 422 (1953).

$\lambda_{max}^{CH_2Cl_2}$ 5.68μ, 5.78μ, 8.28μ(broad) (C, 71.30; H, 8.08; methoxyl, 7.85), which was saponified with 10% ethanolic sodium hydroxide to 17β-methoxy-1,3,5(10)-estratrien-3,16α-diol (IX), m.p. 191°, λ_{max}^{EtOH} 281mμ(ε 2010) (C, 75.27; H, 8.69; methoxyl, 10.59). The diol IX was methylated with diazomethane in dichloromethane-methanol to the synthetic 3,17β-dimethoxy-1,3,5(10)-estratrien-16α-ol (Vb),[7] thin plates, m.p. 165-166°, λ_{max}^{EtOH} 279mμ (ε 1990), 287mμ(ε 1820) (C, 76.03; H, 8.90), identical with the product Va obtained by exhaustive methylation and hydrolysis of estriol glucosiduronic acid II.

We have confirmed the earlier findings of Marrian et al.[2,3] which indicated a partial structure for estriol glucuronide having one alcoholic hydroxyl group combined by a β-glycosidic linkage to a uronic acid, most likely glucuronic acid. On the basis of our evidence we assigned to urinary estriol glucosiduronic acid II, m.p. 221°(dec.), the structure of 3-hydroxy-1,3,5(10)-estratrien-17β-ol-16α-yl-β-D-glucopyranosiduronic acid.

The structures of other glucuronides related to II in human pregnancy urine are being studied.[10]

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[10] This investigation was supported by grants from the American Cancer Society P-265, and the United States Public Health Service.

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THE CONFIGURATION OF ANNOTININE AND SOME REARRANGEMENTS

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(Received 3 March 1961)

IN our full report on the structure of annotinine[1] we deduced the relative configuration portrayed in formula I. The configuration of the methyl group remained undetermined and the argument for the configuration of the oxide ring was not rigorous.

Perry, MacLean and Manske[2] described the transformation of annotinine with phenyl lithium into the diphenyl derivative II. They were able to prove the functionality of II but did not draw any configurational conclusions. The established configuration of the lactone ring[1] and the well-known geometric requirements of a concerted epoxide opening leave no doubt about the exact course of the reaction. The initially formed phenyl ketone must epimerize at the α carbon and then react with a second mole of phenyl lithium

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[1] K. Wiesner, Z. Valenta, W.A. Ayer, L.R. Fowler and J.E. Francis, Tetrahedron 4, 87 (1958).

[2] G.S. Perry, D.B. MacLean and R.H.F. Manske, Canad. J. Chem. 36, 1146 (1958).

to give a diphenylcarbinol which is transformed to II. This reaction proves that the epoxide is cis to the four-membered ring (as in I)[3].

The reaction of oxoannotinine chlorohydrin (III) with phosphorus oxychloride followed by methanol provides a confirmation of this assignment. In addition to oxoanhydroannotinine chlorohydrin[1], formed by a simple β-elimination, we have been able to isolate compound IV, m.p. 229° (Found: C, 49.94; H, 5.85; N, 3.20; P, 4.60; Cl, 8.00; OCH_3, 13.45. $C_{18}H_{25}O_7NPCl$ requires C, 49.83; H, 5.81; N, 3.23; P, 7.14; Cl, 8.17; OCH_3, 14.31%), IR: 1775 cm^{-1} (γ-lactone), 1700 cm^{-1} (five-membered lactam). With the lactam ring in III in the more stable quasi-chair form, the hydroxyl group situated cis to the four-membered ring is antiparallel to the migrating group and the cyclic rearrangement can therefore compete with the normal elimination.

We next turned our attention to the determination of the absolute configuration of annotinine. For this purpose we have determined the rotation dispersion curve[4] of the

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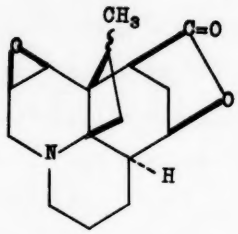
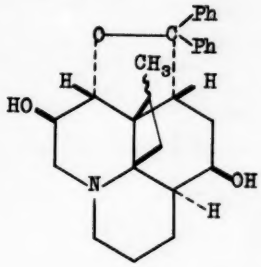
[3] Were the epoxide ring trans to the four-membered ring, a concerted intramolecular attack by the diphenyl carbinol in either configuration would be sterically impossible.

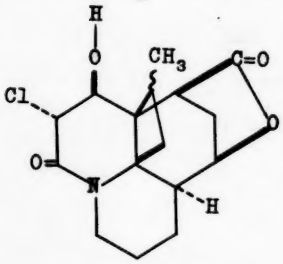
[4] For a summarizing reference, see Carl Djerassi, Optical Rotatory Dispersion. McGraw-Hill Company Inc., New York (1960).



I



II



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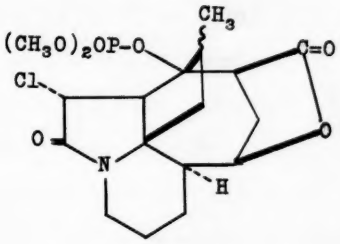
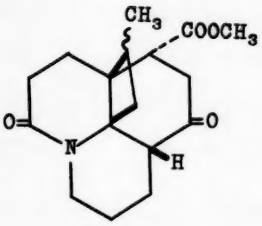
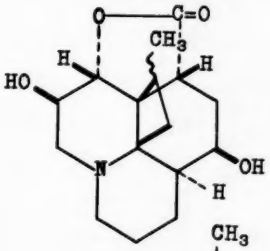


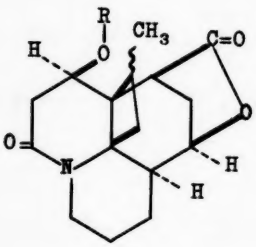
IV



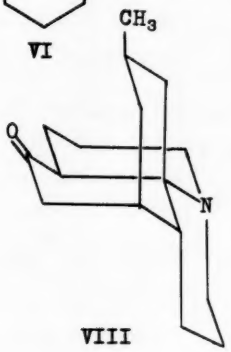
V



VI



VII



VIII

ketoester V[1]. It showed a negative rotation maximum at 322 mμ ($[\alpha] = -3{,}450^{\circ}$) and the application of the octant rule[4,5] to this result led to the absolute configuration given in formula V for this compound. We have checked this result by applying Hudson's lactone rule[6] to annotinine hydrate[1] (VI). The rotation of VI in methanol was $[\alpha]_D = -28.4^{\circ}$. After addition of one mole of KOH and hydrolysis of the lactone, the rotation changed to $[\alpha]_D = -21.6^{\circ}$. Thus, $\Delta[\alpha]_D = -6.8^{\circ}$. Both the lactone and the salt showed monotonous rotation dispersion curves with $\Delta[\alpha]$ negative in the entire region studied ($\Delta[\alpha]_{400\ m\mu} = -40^{\circ}$). This result is to be expected[6] if the absolute configuration is as shown in formula VI.

A third verification of the absolute configuration was accomplished by the application of the Prelog method[7] to the alcohol VII[1] (R=H). The phenylglyoxylic ester of this alcohol (VII, R= $-\overset{\overset{O}{\|}}{C}-\overset{\overset{O}{\|}}{C}-C_6H_5$) gave by treatment with methylmagnesium iodide an excess of negatively rotating atrolactic acid. This result is indicative of the absolute configuration portrayed in the formula VII. If it should appear that

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[5]We wish to thank Dr. Carl Djerassi for a discussion of the dispersion curves.

[6]B. Witkop, Experientia 12, 372 (1956).

[7]V. Prelog, Helv. Chim. Acta, 36, 308 (1953), and following papers.

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the use of three independent methods for the deduction of the absolute configuration is excessive, we would point out that if we base the absolute configuration exclusively on the Hudson rule, then the Prelog method may be regarded as a new and convincing proof of the relative configuration of the hydroxyl in VII (R=H) and consequently of the oxide ring in annotinine. The application of the octant rule to the ketoester V may in turn be regarded as a confirmation of our previous deduction[1] that the asymmetric centre adjacent to the keto group in V has a configuration epimeric to the configuration of this centre in annotinine. Thus, we see that the agreement of various methods of absolute configuration determination is interdependent with the correct assignment of relative configurations to the derivatives used.

Recently, the structure[8] and stereochemistry[9] of lycopodine have been deduced and are represented in formula VIII. Since lycopodine occurs in the same plant as annotinine and the skeleta of the two alkaloids differ only by one carbon-carbon bond, it is very probable that both compounds have the same absolute configuration. We have

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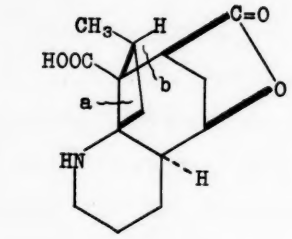
[8] W. A. Harrison and D. B. MacLean, Chem. and Ind. p. 261 (1960).

[9] F.A.L. Anet, Tetrahedron Letters 20, 13 (1960).

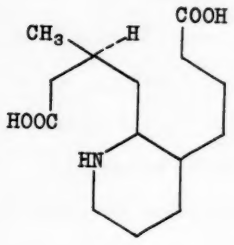
determined the rotation dispersion curve of lycopodine and found a rotation maximum at 307 mμ ($[\alpha] = +2{,}300$). The application of the octant rule[4,5] to this result leads to the absolute configuration of lycopodine shown in formula VIII, which is in agreement with the absolute configuration I for annotinine.

All these results show that annotinine must be represented by the absolute and relative stereostructure I in which the relative configuration of the methyl group is the only unknown feature. In order to determine this last detail we have decided to use the dehydrogenating rearrangement of the amino acid IX to the lactam carboxylic acid XI[1]. This rearrangement had been assumed[1] to proceed by the cleavages (a) and (b) via an intermediate with the gross skeletal structure X.

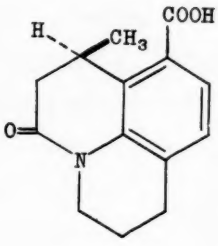
If the relative configuration of the methyl group is as pictured in formula IXa, then the absolute configuration of XI formed by this mechanism must be as given in formula XI. Conversely, the relative configuration of the methyl group as in IXb must, by this mechanism, result in the mirror image of XI. The absolute configuration of compound XI was easily determined by ozonolysis which gave D(+)



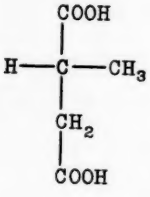
IXa



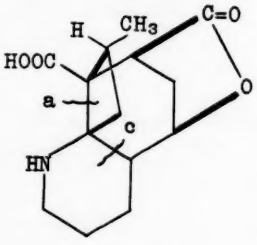
X



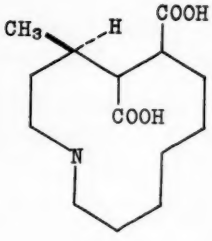
XI



XII D(+)



IXb



XIII

methylsuccinic acid (XII)[10] (m.p. 112°; IR identical with authentic sample $[\alpha]_D$ = +13.1° (ethanol)).

This result seemed to show that the absolute and relative stereostructure of the amino acid IX must be IXa.

In a brilliant X-ray analysis, Przybylska[11] confirmed our structure proposal[12] for annotinine and at the same time derived the relative stereochemistry for this compound. While there is complete agreement in all other respects, the X-ray work postulated that the methyl group of annotinine is cis to the lactone ring. Consequently, if we retain our absolute configuration assignment, the amino acid IX should be portrayed by the formula IXb.

This discrepancy cannot be reconciled and it means that one piece of information (or one assumption) is incorrect. One can, of course, argue that our chemical data are all unexceptional and that, consequently, the relative configuration of the methyl (as in IXb) determined

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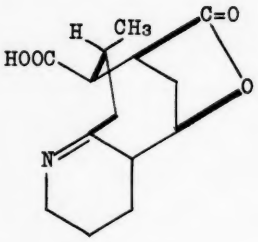
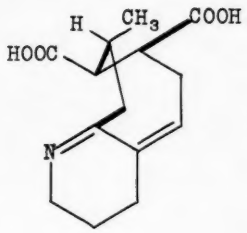
[10] c.f. J. A. Mills and W. Klyne in Progress in Stereochemistry, Edited by W. Klyne, Vol. I. Academic Press Inc., New York, pp. 177-204.

[11] M. Przybylska and L. Marion, Canad. J. Chem. 35, 1075 (1957); M. Przybylska and F. R. Ahmed, Acta Cryst. 11, 718 (1958).

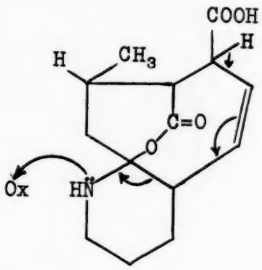
[12] K. Wiesner, Z. Valenta, W.A. Ayer and C. Bankiewicz, Chem. and Ind. 1019 (1956); K. Wiesner, W.A. Ayer, L.R. Fowler and Z. Valenta, Chem. and Ind. 564 (1957).



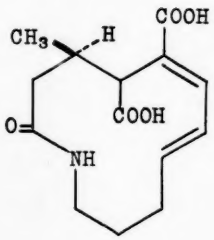
XIV



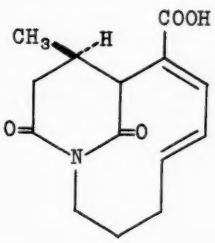
XV



XVI



XVII



XVIII

by the X-ray study is incorrect. A careful analysis shows, however, that the mechanism IX → XI may be the source of the discrepancy. If the configuration of the amino acid is IXb (in agreement with X-ray) and the rearrangement proceeds by the breaks (a) and (c) via an intermediate with the gross structure XIII, the correct enantiomer XI yielding D(+) methylsuccinic acid XII on ozonolysis is obtained. This alternative gross mechanism is consequently compatible with all known chemical and crystallographic data. One of the possible detailed elaborations of this transformation is represented by the structures IXb → XIV → XV → XVI → XVII → XVIII → XI.

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Tetrahedron Letters No. 6, pp. 197-198, 1961. Pergamon Press, Inc. Printed in the United States of America.

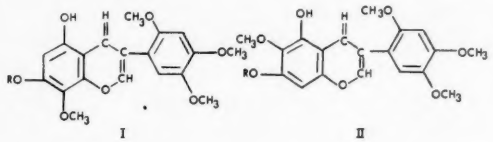
SYNTHESE DES CAVIUNINS

Loránd Farkas und József Várady

aus dem Institut für Organische Chemie der Technischen Universität, Budapest

(Received 9 March 1961)

VER kurzem gelang es Gottlieb und Magalhaes[1] aus dem Holz von Dalbergia nigra Fr. Allem. Caviunin (II; R = H) isolieren und die Struktur von II erklären.



I II

Wir konnten das leicht darstellbare Isocaviunin[2] (I; R = H) benzylieren und in guter Ausbeute (92%) 7-Monobenzyl-isocaviunin(I; R = $C_6H_5CH_2$, Smp. 212-213°, Monoacetat Smp. 183-184°) gewinnen.

Diese Benzyl-Derivat wird bei der Einwirkung von Kaliumäthylat[3] in 87%-iger Ausbeute zum 5-Hydroxy-6,2',4',5'-tetramethoxy-7-benzyloxy-isoflaven (II; R = $C_6H_5CH_2$, Smp. 193-194°, Monoacetat Smp. 175-176°) isomerisiert. Die Entbenzylierung zum Caviunin (II; R = H, Smp. 192-193°, Lit.[1] Smp. 191-193°, Diacetat Smp. 199-200°, Lit.[1] Smp. 198-200°) geschieht auf katalitischem Wege. Das synthetische Caviunin erwies sich auf Grund

[1] O.R. Gottlieb u. M.T. Magalhaes, J.Org.Chem. im Druck. Privatmitteilung von Dr. O.R. Gottlieb 1 März 1961.

[2] L. Farkas u. J. Várady, Acta Chim. Acad.Sci.Hung. im Druck.

[3] L. Farkas u. J. Várady, Chem.Ber. 93, 1269, 2685 (1960); T.R. Seshadri u. H.L. Dhar, Tetrahedron 7, 77 (1959).

aller Eigenschaften mit dem natürlichen Produkt völlig identisch. Eine ausführliche Mitteilung wird in den Chemischen Berichten veröffentlicht werden.

An dieser Stelle danken wir Herrn Dr. O.R. Gottlieb (Rio de Janeiro) für das natürliche Caviunin.

196

Tetrahedron Letters No. 6, pp. 199-205, 1961. Pergamon Press, Inc. Printed in the United States of America.

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NEW CLASSES OF PHOSPHORUS-CONTAINING DYES

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Chemical Research Laboratories, Gevaert Photo-Producten N.V.

Mortsel, Belgium

(Received 6 March 1961)

IN the course of a research program for photographic sensitizing dyes, a new class of dyes containing a $C{=}P\langle$ auxochrome has been discovered. It may be subdivised into several subclasses.[1] It is our intention, in this preliminary communication, to bring a short record of the principal routes by which the new dyes may be obtained.

A first class of new phosphorus-containing dyes, which we propose to call "phosphinines", by analogy with the structurally related cyanine dyes, is characterized by the auxochromophoric system:

$$\rangle P{=}\overset{|}{C}\text{-}(CH{=}CH)_n - CH{=}\overset{|}{C}\text{-}\overset{+}{P}\langle \longleftrightarrow \rangle \overset{+}{P}\text{-}\overset{|}{C}{=}(CH\text{-}CH)_n = CH\text{-}\overset{|}{C}{=}P\langle$$

These new dyes may be synthesized in a variety of ways. Starting with cyclopentadienylene-triphenylphosphorane (I), whose nucleophilic properties have been pointed out recently by Ramirez and Levy[2], the symmetrical dye II may be obtained, e.g. by refluxing with ethyl orthoformate or orthoacetate in acetic anhydride.

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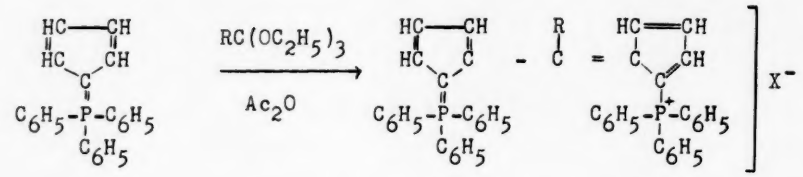
[1] Gevaert, Belg.Pat. 583.922 (prior. G.-B. 24.10.58) and A.Van Dormael, J.Nys and H. Depoorter, Sci. & Ind. Phot. (2) 31, 389 (1960)

[2] F. Ramirez and S. Levy, J.Amer.Chem. Soc. 79, 6167 (1957)



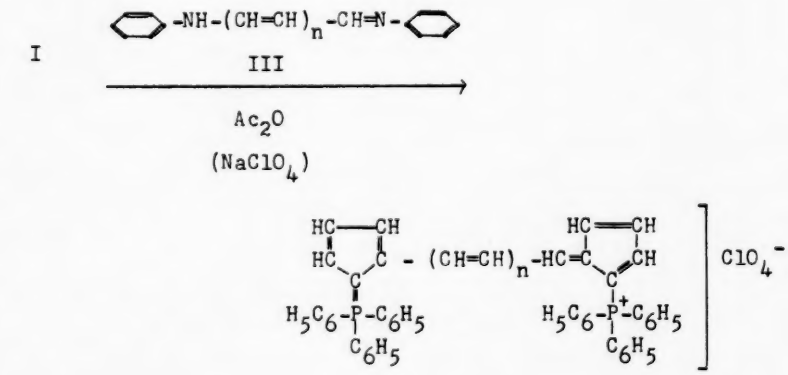
I II

II : R = H; X^- = I^-; λ_{max} = 477 mμ *

II : R = CH_3; X^- = ClO_4^-; λ_{max} = 488 mμ

It will be noticed that the introduction of a methyl-group in the methine link results in a bathochromic shift, analogously to the shift which was observed by Brunings and Corwin[3] in the same conditions with dipyrrylmethene dyes.

The same cyclopentadienylene-phosphorane I condensed with β-anilino acrolein anil (III, n = 1) leads to the corresponding dye IV (n = 1) with a trimethine link between both nuclei.



IV

* All optical data were determined in ethanolic solution.

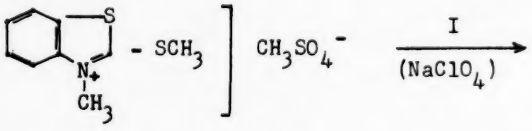
[3] K.J. Brunings and A.H. Corwin, J. Amer. Chem. Soc. 64, 593 (1942)

The phosphorane I yields the corresponding pentamethine homologue IV (n = 2) by reaction with the anil of 1-anilino-pentadien(1,3)-al(5) (III, n = 2). The absorption data are : dye IV (n = 1), λ_{max} = 597 mμ and dye IV (n = 2), λ_{max} = 695 mμ.

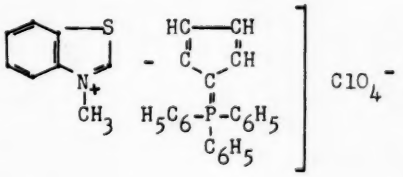
Furthermore, the cyclopentadienylene-phosphorane I, when allowed to react with various electrophilic reagents ordinarily used in the chemistry of cyanine and merocyanine dyes, yields asymmetrical dyes which we might call "phosphocyanines", characterized by the following auxochromophoric system :

$$\geqslant P=\overset{|}{C}-(CH=CH)_n-CH=\overset{|}{\underset{+}{N}}- \longleftrightarrow \geqslant P-\overset{|}{\underset{+}{C}}=(CH-CH)_n=CH-\overset{|}{N}-$$

As an example, I reacts with 2-methylmercapto-3-methyl-benzothiazolium methylsulphate (V) in ethanol to produce the dye VI (λ_{max} = 398 mμ). The reaction is catalyzed by triethylamine.

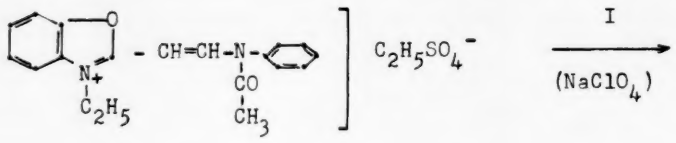


V

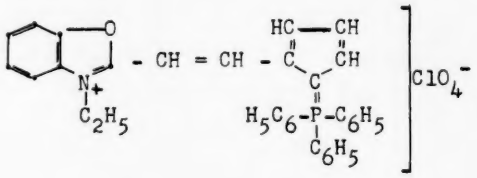


VI

Similarly, the reaction of (I) with 2-(β-acetanilido-vinyl)-3-ethyl-benzoxazolium ethylsulphate (VII) yields the dye VIII (λ_{max} = 480 mμ).

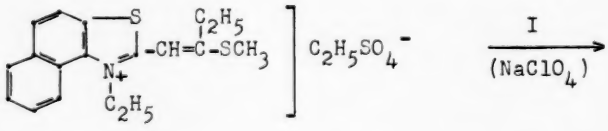


VII

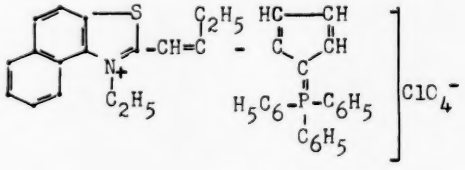


VIII

Chain-substituted phospho-cyanine dyes may be obtained by using β-alkyl-β-methylmercaptovinyl derivatives such as IX whereby dye X (λ_{max} = 542 mμ) is obtained.



IX

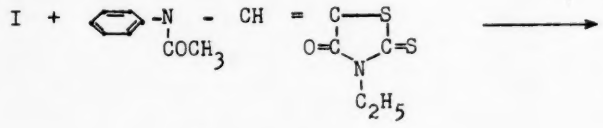


X

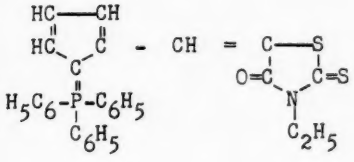
The cyclopentadienylene-phosphorane I also reacts with acetanilidomethylene derivatives of ketomethylene nuclei in the presence of acetic anhydride, whereby merocyanine-like systems are obtained, for which the name "merophosphinines" is proposed.

These dyes, too, display a new characteristic auxochromophoric pattern, namely :

Thus, reaction of I with the rhodanine-intermediate XI yields the new dye XII (λ_{max} = 486 mμ).

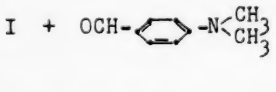


XI

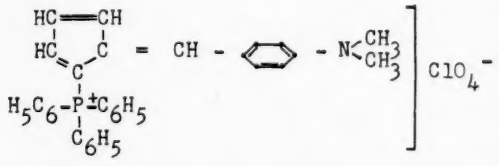


XII

Aromatic aldehydes react with I in appropriate conditions (refluxing in acetic anhydride) to yield another new series of polymethine dyes. With p -dimethylaminobenzaldehyde (XIII), e.g. dye XIV is obtained (λ_{max} = 495 mμ).

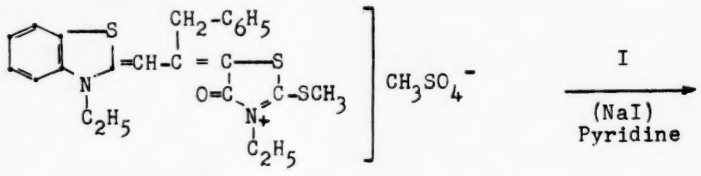


XIII

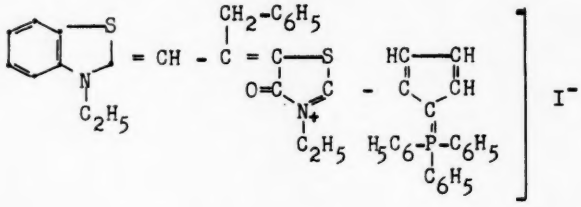


XIV

Still more complex dye-systems may be synthesized. As an example, starting from the quaternized merocyanine dye XV, the complex dye XVI (λ_{max} = 606 mμ) is obtained by reaction with I in pyridine.

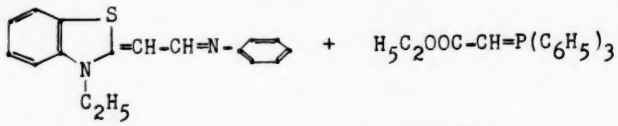


XV



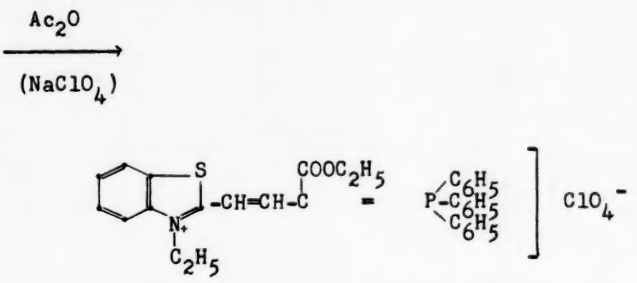
XVI

Finally, instead of cyclopentadienylene-triphenyl-phosphorane (I), other phosphoranes such as carbethoxymethylene-triphenyl-phosphorane[4] (XVII) may be used. By reaction with the anil of 2-formylmethylene-3-ethyl-benzothiazoline (XVIII) in acetic anhydride, dye XIX is obtained (λ_{max} = 446 mμ).



XVIII XVII

[4] O. Isler, H. Guttmann, M. Montavon, R.Ruegg, G. Ryser and P.Zeller, Helv. Chim. Acta 40, 1242 (1957).



XIX

A detailed description of the synthesis and the properties of the new dyes will be published elsewhere,[5] whilst the optical data of some of these dyes have been discussed recently.[6]

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[5] H. Depoorter, J. Nys and A. Van Dormael, Bull.Soc.Chim.Belg. in preparation.

[6] A. Van Dormael, Chimia 15, 67 (1961).

Tetrahedron Letters No. 6, pp. 206-210, 1961. Pergamon Press, Inc. Printed in the United States of America.

THE STRUCTURE OF CATHARANTHINE, A NOVEL VARIANT OF THE IBOGA ALKALOIDS[1,2]

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(Received 14 February 1961; in revised form 3 March 1961)

Catharanthine (I), a $C_{21}H_{24}O_2N_2$ pentacyclic indole alkaloid from Vinca rosea Linn., has been shown to contain a carbomethoxy group and an isolated double bond.[3,4] Dihydrocatharanthine (II) was obtained by catalytic hydrogenation of catharanthine at atmospheric pressure (PtO_2 in alcohol), $C_{21}H_{26}O_2N_2$,[5] m.p. 63-65°, $[\alpha]_D^{26}$ = +33° ($CHCl_3$); hydrochloride, $C_{21}H_{26}O_2N_2 \cdot HCl$, m.p. 216-221° (d.), $[\alpha]_D^{26}$ = +44° (CH_3OH).

Treatment of dihydrocatharanthine under reflux with hydrazine in absolute ethanol resulted in decarboxylation in a manner analogous to that reported for voacangine (III) and related alkaloids.[6]

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[1] Presented in part as Vinca Alkaloids VII before the Organic Section of the 138th National Meeting of the American Chemical Society, New York, N.Y., September 11-16, 1960.

[2] Paper VI, N. Neuss, M. Gorman and G. H. Svoboda, Chemistry of Some Vinca Alkaloids, Plant Chemists Meeting, Columbia University, February 12, 1960, New York.

[3] Marvin Gorman, Norbert Neuss, Gordon H, Svoboda, Albert J. Barnes, Jr., and Nancy J. Cone, J. Am. Pharm. Assoc. Sci. Ed. 48, 256 (1959).

[4] Marvin Gorman, Norbert Neuss and Gordon H. Svoboda, J. Am. Chem. Soc. 81, 4745 (1959).

[5] Satisfactory analyses have been obtained for all compounds for which molecular formulae are given.

[6] U. Renner, D. A. Prins and W. G. Stoll, Helv. Chem. Acta 42, 1572 (1959).

The new descarbomethoxy base, epi-ibogamine (IV), $C_{19}H_{24}N_2$, m.p. 162-164° (from ether or ethyl acetate) was further characterized as the hydrochloride $C_{19}H_{24}N_2 \cdot HCl$, m.p. 183-188°, $[\alpha]_D^{25}$ = +86° (CH_3OH).

The position of the carbomethoxyl at C_{18} was also shown by the formation of the tetrahydro-1,3-oxazine (V)[7] of catharanthinol (VI), the $LiAlH_4$ reduction product of (I). This derivative was obtained by the treatment of VI with dry hydrogen chloride in acetone.[7] As expected, the compound does not have any NH-indole or OH absorption in the infrared spectrum; $C_{23}H_{28}ON_2$, m.p. 188-191°.

The relationship of catharanthine and its derivatives to the corresponding Iboga alkaloids[8] [e.g. ibogamine (VII) and coronaridine[9] (carbomethoxyibogamine, VIII)] was indicated from the similarities of their infrared spectra and finally proven by the isolation of the indoloquinoline (IX) from the selenium dehydrogenation of epi-ibogamine. This product (IX) was found to be identical in every respect (X-ray powder pattern, I.R., U.V., and mass spectra) with an authentic sample obtained by dehydrogenation of ibogamine (VII).[8, 10]

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[7] Prepared analogously to tetrahydro-1,3-oxazine of voacangarine alcohol, D. Stauffacher and E. Seebeck, Helv. Chim. Acta 41, 169 (1959).

[8] M. F. Bartlett, D. F. Dickel and W. I. Taylor, J. Am. Chem. Soc. 80, 126 (1958).

[9] Marvin Gorman, Norbert Neuss, Nancy J. Cone and James A. Deyrup, ibid. 82, 1142 (1960).

[10] We gratefully acknowledge a detailed description of the conditions of this reaction[8] as well as a sample of authentic indoloquinoline from Dr. W. I. Taylor. We also thank Prof. Biemann of M.I.T. for the mass spectra reported herein.

The position of the endocyclic double bond was indicated by the NMR spectrum of catharanthine (I) which has shown the presence of an ethyl group (methyl triplet centered at 8.90τ with peaks separated by 7 c.p.s.) and a single proton on a double bond (peak at 4.10τ).[11] The position of the double bond was corroborated by products resulting from dehydrogenation of catharanthine (I) and dihydrocatharanthine (II) using Pd on carbon.

The former gave at 150-160° a good yield of 3-ethyl pyridine,[12] while the latter required a temperature of 230-250° to afford 3-methyl-5-ethyl pyridine[12] in a manner similar to that previously described for voacangine[13] (III). The formation of 3-ethyl pyridine is explained by the fission of the C_1-C_2 allylic bond, while in dihydrocatharanthine (II) the bond breaks as in voacangine (III) between C_1 and C_{18}.[13]

The hydrogenation of catharanthine led to only one isomer (vide supra). From the models of I, it is apparent that the hydrogen must come in from the side nearest to N_b to give the axial ethyl group shown in II. Therefore, dihydrocatharanthine (II) and epi-ibogamine (IV) are epimeric at C_4 with coronaridine (VIII) and ibogamine (VII), respectively, since the

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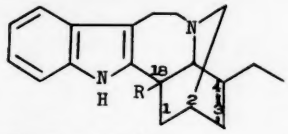
[11] We should like to thank Prof. J. C. Martin, University of Illinois for the interpretation of the NMR spectra.

[12] We wish to thank Dr. S. E. Cislak of Reilly Tar and Chemical Corp., Indianapolis, for authentic samples of the above bases. The identification was made through VPC and X-ray powder patterns of the corresponding picrates.

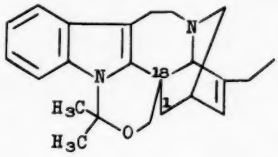
[13] F. Walls, O. Collera and A. Sandoval, Tetrahedron 2, 173 (1958).

C-ethyl group in the Iboga alkaloids (e.g. ibogaine X) has been shown to be equatorial,[14] and catharanthine must be Δ^3-dehydrocoronaridine.

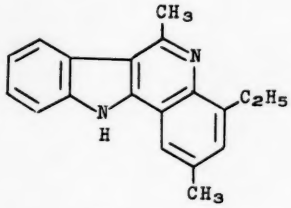


I R = $COOCH_3$

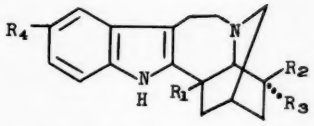
VI R = CH_2OH



V



IX



II, III, IV, VII, VIII, X

II R_1=$COOCH_3$; R_2=H; R_3=C_2H_5; R_4=H; Dihydrocatharanthine

III R_1=$COOCH_3$; R_2=C_2H_5; R_3=H; R_4=OCH_3; Voacangine

IV R_1=H; R_2=H; R_3=C_2H_5; R_4=H; Epi-ibogamine

VII R_1=H; R_2=C_2H_5; R_3=H; R_4=H; Ibogamine

VIII R_1=$COOCH_3$; R_2=C_2H_5; R_3=H; R_4=H; Coronaridine

X R_1=H; R_2=C_2H_5; R_3=H; R_4=OCH_3; Ibogaine

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[14] G. A. Jeffrey, Gerda Arai and J. Coppola, Abstract of paper presented at American Crystallographic Assoc. Meeting, Cornell, July 19-24, 1959.

Acknowledgment: We should like to thank the following individuals for their help in this investigation: Mr. A. J. Barnes, Jr., supply of crude catharanthine; Mrs. Nancy J. Cone, laboratory assistance; Dr. H. E. Boaz, infrared spectra; Mr. L. G. Howard, ultraviolet spectra; and Messrs. G. M. Maciak, R. Hughes, and W. L. Brown, microanalyses.

1961

Tetrahedron Letters No. 6, pp. 211-215, 1961. Pergamon Press, Inc. Printed in the United States of America.

EFFECT OF STRUCTURAL CHANGES IN REACTANTS ON THE STRUCTURE OF TRANSITION STATES[1]

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Cambridge, Massachusetts

(Received 8 March 1961)

A central problem in the theoretical calculation of relative rates is one of estimating the change in structure of the transition state caused by a change in structure of one of the reactants. The following rule is proposed for predicting the direction of the effect of a change of a group in a reactant on the structure of the transition state. Reacting bonds (bonds being made or broken) are defined as σ- or π-bonds present in the transition state but absent in either reactants or products. Radiating from the group, star the nearest reacting bond or bonds and every alternate more remote such bond, except bonds to or within substituted aryl groups.[2] The starred reacting bonds are lengthened at the transition state by electron-supplying groups and shortened by electron-attracting groups. The opposite is true for unstarred reacting bonds. The rule will be illustrated by examples.

In the solvolysis of cumyl chlorides, the rule predicts that p- or m-methyl should increase the extent of C–Cl cleavage at the transition state, while p- or m-chloro should do the reverse.

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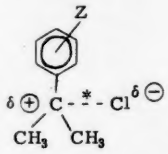
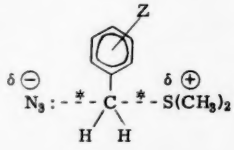
1 Supported in part by the National Institutes of Health through Research Grant RG-3711 and by a postdoctoral fellowship to E. R. T. from the Division of General Medical Services, U. S. Public Health Service.

2 This gives the same predictions as starring all non-reacting π-bonds which are within the group or between the group and a reacting bond and which have π-overlap with the reacting bond at the transition state, and not starring reacting π-bonds adjacent to starred non-reacting π-bonds. In even-membered cyclic systems of reacting bonds, the effect along the shortest path will prevail.



Experimentally the sensitivity to solvent polarity (ratio of rates at 25°, methanol to ethanol or ethanol to 2-propanol) is larger for m-methyl and p-phenyl, but less for p- or m-chloro, p-carbomethoxy or p-trifluoromethyl.[3] This confirms that there is more complete ionization at the transition state when electron-supplying substituents are present. Thus the rule fares better here than usual extensions of the Hammond postulate: that the carbonium ion should be the best model for the transition state when least stabilized, but if both are more stable the transition state should be reached sooner, before there is as much movement along the reaction coordinate.[4,5]

The reaction of sodium azide with substituted benzyldimethylsulfonium p-toluenesulfonates is near the other mechanistic extreme, since it involves a strong nucleophile but poor leaving group. Here N–C bond formation should be more complete with electron-attracting substituents.



The ratio of second-order rate constants at 60° in 80% dioxane-20% water vs. 100% water decreases in the order m-chloro (240), unsubstituted (200), p-methyl (115), showing that charge recombination is indeed more complete when

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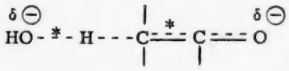
3 Y. Okamoto T. Inukai and H. C. Brown, J. Am. Chem. Soc. 80, 4975 (1958).

4 G. S. Hammond, J. Am. Chem. Soc. 77, 334 (1955).

5 K. B. Wiberg, Chem. Revs. 55, 733, 737 (1955).

electron-attracting substituents are present.[6] In the closely similar reaction with sodium hydroxide (instead of azide) in water at 60° the sulfur isotope effect is larger for p-methyl (1.0096) than for unsubstituted (1.0093) or m-chloro (1.0082),[7] again as predicted.

Enolizations of ketones catalyzed by acids or nucleophiles have transition states generally closer to products (enol or enolate ion and conjugate acid of the base) than to reactants as shown by the relatively large magnitudes of solvent (H_2O vs. D_2O) isotope effects when water or hydroxide ion is the nucleophile.[8] However, the strongest bond to the α-hydrogen (the one to oxygen) should be weaker and hence the α-hydrogen isotope effect k_H/k_D should be greater the stronger the base used. Because hydroxide lacks the extra electron-attracting proton of water, it should give a longer O---H bond and larger α-hydrogen isotope effect.



A symmetrical transition state gives maximum isotope effect because it has no vibration of the α-hydrogen to offset than in the ground state in either the asymmetric or symmetric stretch. There is in fact a progressive increase in this isotope effect from water to acetate ion to hydroxide ion for ionization of either nitromethane[9] or α-phenylisocaprophenone.[10] This is contrary to the Wiberg rule.[5]

Evidence for the alternating effect is derived from several reactions.

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6 C. G. Swain, T. Rees and L. J. Taylor, paper to be published. The ratio k/k° in water was 2.2 for p-methyl, 0.73 for m-chloro.

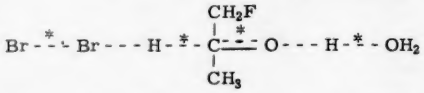
7 C. G. Swain and E. R. Thornton, paper to be published. The product alcohols were isolated in good yields. The ratio k/k° was 1.62 for p-methyl, 1.57 for m-chloro.

8 C. G. Swain and R. F. W. Bader, Tetrahedron 10, 182 (1960); C. G. Swain, R. F. W. Bader and E. R. Thornton, ibid. 10, 200 (1960); C. G. Swain and E. R. Thornton, two papers submitted for publication; C. G. Swain and A. S. Rosenberg, J. Am. Chem. Soc. 83 (1961), in press.

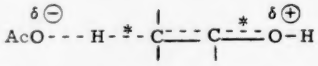
9 O. Reitz, Z. physik. Chem. A176, 363 (1936).

10 C. G. Swain, E. C. Stivers, J. F. Reuwer, Jr. and L. J. Schaad, J. Am. Chem. Soc. 80, 5885 (1958).

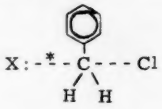
The OH isotope effect is larger for bromine oxidation of 1-fluoro-2-propanol than of 2-propanol in water solution, suggesting more complete OH bond breaking with the fluorine substituent.[11] The CH isotope effect is smaller. The CH/CT isotope effect for enolization of α-phenylisocaprophenone is larger for



acetic acid catalysis (11.4) than for acetate ion catalysis (10.2),[10] because the AcO^- - - - H bond is longer with the electron-attracting proton "group" on the carbonyl oxygen in place of no group.



The Cl^{35}/Cl^{37} isotope effect for reaction of nucleophiles with benzyl chloride at 30° in 80% dioxane–20% water by weight is larger with water (1.0074) than with the stronger nucleophiles cyanide ion (1.0068) or thiosulfate ion (1.0060).[12]



The transition state for

$$X + YX \longrightarrow XY + X$$

should be close to symmetrical, i.e. the X - - - Y bond lengths should be nearly identical. The rule then predicts transition states resembling reactants more than products for the polar displacements

$$Z + YX \longrightarrow ZY + X$$

$$X + YZ \longrightarrow XY + Z$$

where Z is better than X as a nucleophile or leaving group respectively. A better nucleophile need not "push so hard" or a better leaving group needs

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11 C. G. Swain, R. A. Wiles and R. F. W. Bader, J. Am. Chem. Soc. 83 (1961), in press.

12 J. W. Hill, "Chlorine Isotope Effects in the Reactions of Benzyl and Substituted Benzyl Chlorides with Various Nucleophiles," Ph.D. thesis, Univ. of Arkansas, 1961, p. 101. We are indebted to Prof. Arthur Fry for a copy of this thesis.

"less of a push" to reach the free energy maximum. For example, the reaction of hydroxide ion with a sulfonium ion should have a transition state close to reactants because hydroxide ion Z is a stronger nucleophile than a neutral sulfide X (or because the dialkyl sulfide Z is a better leaving group than hydroxide ion X). The solvent isotope effect k_{H_2O}/k_{D_2O} with p-methylbenzyldimethylsulfonium p-toluenesulfonate in water at 60° is 0.99, confirming that hydroxide is only very loosely bonded at the transition state.[8]

Because different bonds may be affected differently, effects on rate or activation energy may be composites of opposing contributions. Effects on particular bonds are therefore best examined through isotope effects by successive multiple isotopic substitution.

Tetrahedron Letters No. 6, pp. 216-222, 1961. Pergamon Press, Inc. Printed in the United States of America.

STRUCTURE OF HIMACHALENES

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Bangalore, India

National Chemical Laboratory, Poona, India

(Received 6 March 1961)

THE essential oil from Himalayan deodar (Cedrus deodara, Loud.) has been shown[1] to contain two sesquiterpene hydrocarbons, namely α - and β-himachalenes. We now report on their structure which confirms our original contention[1] that these hydrocarbons represent a new framework for sesquiterpenes.

The purified samples** of these hydrocarbons had the following constants: α-himachalene+ b.p.93-94°/2 mm, n_D^{25} 1.5082, d_4^{25} 0.9206, M_D 65.85, $[\alpha]_D^{25}$ -187.1° (clean), $[\alpha]_D^{25}$ -192.3° (4.16% in $CHCl_3$); β-himachalene, b.p. 121-22°/4 mm, n_D^{25} 1.5130, d_4^{25} 0.9330, M_D 65.71, $[\alpha]_D^{25}$ + 225.8° (clean), $[\alpha]_D^{25}$ + 224.7° (4.76% in $CHCl_3$). Though the experimental values for molecular refractivity are lower than those calculated (66.13) for $C_{15}H_{24}$, the bicyclic nature of these compounds is confirmed by quantitative hydrogenation (AcOH and PtO_2 catalyst), and percamphoric acid titrations, as both of these methods showed the presence of two ethylenic linkages in the

* Present address: Division of Organic Chemistry, National Chemical Laboratory, Poona, India.

** Vapour Phase Chromatography showed a single peak in each case. The details of vapour phase chromatographies discussed in this communication will be described in the full paper.

\+ All compounds analysed correctly.

[1] G.S. Krishna Rao, Sukh Dev and P.C. Guha, J.Ind.Chem.Soc. 29, 721 (1952).

molecule. α-Himachalene yielded a crystalline di-α-epoxide, m.p.125-126°, $[\alpha]_D^{30}$ -144° (1.25% in $CHCl_3$), while the β-isomer furnished only a liquid product, b.p.126-30°/2 mm, n_D^{26} 1.4939, $[\alpha]_D^{26}$ + 87° (2% in $CHCl_3$).

In the infrared, α-himachalene displayed bands assignable to $\rangle C{=}CH_2$ (3060, 1770, 1625, 885 cm^{-1}) and $\rangle C{=}C\langle_H$ (1665, 865 cm^{-1} ?), and three peaks at 1388, 1377 and 1362 cm^{-1} due to methyl and gem-dimethyl groups. The β-isomer showed bands due to a trisubstituted olefinic linkage only (1665, 857 cm^{-1} ?), a gem-dimethyl group (1360 cm^{-1}) also being present. Since both hydrocarbons yield the same crystalline dihydrochloride[1*], the asymmetric di-substituted ethylenic bond of α-himachalene is replaced by a tri- or tetra-substituted olefinic function in the β-isomer. A decision on this point could be arrived at by a study of their nuclear magnetic resonance (NMR) spectra.** On the lower field-strength side α-himachalene showed two peaks at -45 (singlet) and +1 cps (partly split) corresponding in intensity to one and two protons respectively, and readily assignable[2] to a trisubstituted and disubstituted ethylenic linkage; these assignments were confirmed by a study of the infra-red and NMR spectra of dihydro-α-himachalene (by the hydrogenation of α-himachalene over PtO_2 catalyst in ethanol: b.p.98-100°/1 mm, n_D^{24} 1.4972, d_4^{24} 0.9105, $[\alpha]_D^{24}$ + 59.2° in $CHCl_3$ solution). β-Himachalene displayed only one peak in this region at -37 cps and corresponded to one proton in its intensity; clearly the other ethylenic linkage in this isomer is tetrasubstituted.

* Nil optical rotations recorded for both the dihydrochloride and the monohydrochloride are in error. These compounds are optically active: dihydrochloride, $[\alpha]_D^{30}$ + 22° (9.6% in $CHCl_3$); monohydrochloride, $[\alpha]_D^{30}$ + 113° (2.5% in $CHCl_3$).

** All proton magnetic resonance spectra were determined at 60 mc rf. on 25 per cent solutions in CCl_4. The chemical shifts are herein reported in cycles per second relative to water (zero standard).

[2] e.g. see: Sukh Dev, Tetrahedron 9, 1 (1960).

The total number of methyl groups in these molecules have been estimated by quantitative infra-red absorption[3,4,5] and the values correspond approximately to three for α-himachalene and four for β-himachalene. This is confirmed and further elaborated by the NMR data: α-himachalene, sharp peaks at 236, 234 and 183 cps, each corresponding in intensity to three protons and assignable[2] to two methyl groups on a sp^3 carbon (s) and one methyl group on an olefinic bond; β-himachalene displayed two 'saturated methyl' proton peaks (246,231 cps) and one 'unsaturated methyl' proton peak (185 cps), the first two each corresponding in area to three protons, while 185 cps peak accounting for six protons.

The infra-red spectra of tetrahydro-α-(b.p. 132°/14 mm, n_D^{24} 1.4862, d_4^{24} 0.8986, M_D 66.48, $[\alpha]_D^{24}$ -8.25° in $CHCl_3$ solution) and tetrahydro-β-himachalene (b.p. 110-111°/3 mm, n_D^{26} 1.4875, d_4^{26} 0.8997, M_D 66.65, $[\alpha]_D^{26}$ -21.1° in $CHCl_3$), though quite similar, showed important differences in the intensities of several bands in the fingerprint region. This is readily explainable on the basis of formation of differing amounts of stereoisomers during hydrogenation. The vapour-phase chromatography (VPC) of the products, disclosed in each case at least two components; the component with lower retention time being present to the extent of 15% in the case of α-isomer and 66% in the β-isomer. The infra-red spectra and the physical constants differed from those recorded for several known perhydro bicyclic sesquiterpene systems[6,7].

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[3] S.A. Francis, J.Chem. Phys. 18, 861 (1950).

[4] D.H.R. Barton, J.E. Page and E.W. Warnhoff, J.Chem. Soc. 2715 (1954)

[5] L. Henry and G. Ourisson, Bull.Soc. Chim. Fr. 99 (1955)

[6] J. Pliva and F.Šorm, Coll.Czech.Chem.Comm. 14, 274 (1949).

[7] J. Pliva, V.Herout, B. Schneider and F.Šorm, Coll.Czech.Chem.Comm. 18, 500 (1953).

Himachalenes* on selenium-dehydrogenation (305-310°; 48 hours) yielded three main products, two of these were readily identified as cadalene (I) (from the highest boiling fraction b.p.145-155°/11 mm; characterized by its ultra-violet spectrum, and trinitrobenzene complex, m.p. and mixed m.p. with an authentic sample 110-111°) and 2-methyl-6-(p-tolyl)-heptane (II) (from the lowest boiling fraction b.p.128-35°/11 mm; a purified sample had: b.p. 125-26°/11 mm, n_D^{26} 1.4887, d_4^{26} 0.8678, $\lambda_{max}^{heptane}$ 260, 265 and 273 mμ. The compound on chromic acid oxidation yielded terephthalic acid. The infra-red spectrum was identical with that of an authentic material[8] prepared from bisabolene). The third product, which has not, so far, been obtained free from (II) is a new sesquiterpene-dehydrogenation product (III) and as will be shown in the sequel is characteristic of the himachalenes ring-skeleton. The percentage composition of the Se-dehydrogenation product was estimated by VPC to be 30% (I), 39% (II) and 28% (III). Since a cadalenic sesquiterpene is hardly expected to undergo cleavage to yield (II), it was argued that himachalenes have a carbon-skeleton capable of scission to an intermediate that can, later, give rise to both (I) and (II). This is supported by the results of sulphur-dehydrogenation (210-15°; 2 hr) of himachalenes. The products of S-dehydrogenation were found to consist of 56% (II) and 33% (III), only traces of cadalene (less than 5%, as revealed by VPC and confirmed by quantitative absorption at 325 mμ, the longest wavelength band of cadalene) were formed; clearly cadalene arises by a recyclization or a similar reaction.[9] A central cut

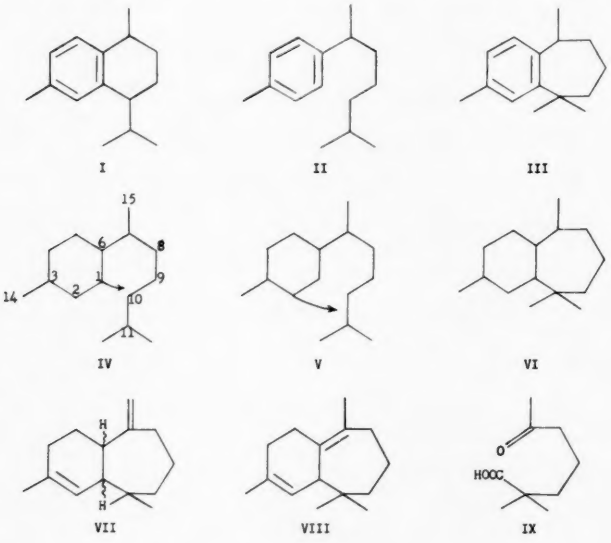
* Since both α- and β-himachalenes on Se-dehydrogenation yielded essentially the same products, further dehydrogenation experiments were carried out on the mixture of hydrocarbons which was more easily accessible.

8 L. Ruzicka and Van Veen, Liebigs Ann. 468, 133 (1929)

9 L. Ruzicka, J.Meyer and M.Mingazzini, Helv.Chim.Acta 5, 345 (1922)

of S-dehydrogenation product, consisting chiefly of (II) and (III) (~ 1:1) was examined in the 1650-1950 cm^{-1} region to reveal the characteristic benzene-substitution patterns[10] and the results compared with similar absorption patterns, obtained under identical conditions for (II) and 2-methyl-benzosuberane. These data clearly indicate that compound (III) is a 1,2,4-trisubstituted benzene, as the pattern was a summation of (II) and 2-methylbenzosuberane patterns. This was confirmed by the nitric acid oxidation of this cut, when both terephthalic acid and trimellitic acid (anhydride, m.p. 161-162°, mixed m.p. with an authentic sample 162-163°) were obtained in approx. equal amounts.

Taking into consideration all the experimental results discussed above, it becomes apparent that himachalenes have the carbon-skeleton (IV), with carbon 1 attached to a position on the other part of the molecule. Noting the fact that β-himachalene has a tetra-substituted ethylenic linkage which



[10] C.W. Young, R.B. DuVall and N.Wright, Analyt.Chem. 23, 709 (1951)

becomes asymmetric disubstituted in α-himachalene, and further bearing in mind the nature of the methyl groups, the linkage in (IV) must be between C_1 and C_{11}; structure (V) stands ruled out as it would have one terminus of the tetrasubstituted ethylenic linkage in β-himachalene at a bridge-head, and this is sterically prohibitive. In order to gain experimental evidence in favour of C_1—C_{11} linkage, nitric acid oxidation of himachalenes was investigated. The composition of the product (as methyl esters; b.p.70-110°/10 mm; yield ~3.5 g/13 g of himachalenes) was determined by a combination of VPC, fractionation, and actual isolation (partitition chromatography) and characterization (by comparison with authentic samples) of acids to be: dimethyl malonic (4%), α,α-dimethyl succinic (20%), α,α-dimethyl-glutaric (38%), α,α-dimethyl adipic (13%) and succinic acid (25%). These results clearly show the carbon framework of himachalenes as (VI), and then the new dehydrogenation product (III)* can possibly be assigned the structure shown.

α- and β-Himachalenes can now be represented by the structures (VII) and (VIII) respectively. These structures have been preferred over the alternate structures* with the trisubstituted ethylenic linkage in the 3,4-position, because of the formation of significant amounts of succinic acid during the nitric acid oxidation. The structure (VIII) for β-himachalene has been further confirmed by oxidative ozonolysis when the acidic products were identified as laevulinic and geronic acid (IX; Me ester, b.p.105-6°/10 mm, n_D^{24} 1.4400; semicarbazone of methyl ester, m.p. with an authentic sample[11] 156-57°, the infra-red spectra of the two

* Though a decision between these alternatives should be possible on the basis of NMR data, the treatment is inconclusive and will be discussed fully in the detailed paper.

[11] H.H. Strain, J. Biol. Chem. 102, 137 (1933).

samples were superimposable); these products can only arise from structure (VIII).

Further work relating to α-himachalene and stereochemistry, and the biogenetic implications of these structures will be discussed in the fuller paper.

Acknowledgements:- The authors are grateful to Dr. Leo Levi and Dr. G.S. Krishna Rao for the NMR and several infra-red spectra.

1961

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SYNTHESIS OF ERYTHROCENTAURIN SEMICARBAZONE

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(Received 21 March 1961)

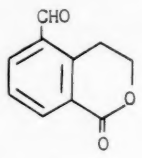
IN a previous communication,[1] we proposed the structure I for erythrocentaurin, which was produced by hydrolysis of swertiamarin with emulsin.[2] At that time, however, we could not exclude the structure II, as an alternative possibility. This communication describes the confirmation of the structure of erythrocentaurin by the synthesis of I, semicarbazone.

The course of the synthesis is illustrated in the following scheme: (V): $C_{11}H_{10}O_3$, m.p. 102-103°, (Found: C, 69.09; H, 5.48. Calc.: C, 69.46; H, 5.30) I.R. spectrum, 5.81, 5.91 . (VI): $C_{10}H_8O_3$, m.p. 225-226°, (Found: C, 68.04; H, 4.70. Calc.: C, 68.18; H, 4.58). (VII): $C_{10}H_8O_6$, m.p. 214-215°, (Found: C, 53.68; H, 4.02. Calc.: C, 53.58; H, 3.68) trimethylester, $C_{13}H_{14}O_6$, m.p. 108-109°, (Found: C, 58.49; H, 5.41. Calc.: C, 58.64; H, 5.30). (VIII): $C_{10}H_{14}O_3.H_2O$, m.p. 104-105°, (Found: C, 60.21; H, 8.31. Calc.: C, 59.98; H, 8.05), which is identical with the triol[1] from erythrocentaurin in I.R. spectrum and mixed m.p. (IX): $C_{10}H_8O_4$, m.p. 239-240°, (Found: C, 62.50; H, 4.52. Calc.: C, 62.50; H, 4.20), which is identical with the lactone carboxylic acid[1] from erythrocentaurin in I.R. spectrum and mixed m.p. (XI): (semicarbazone of I), m.p. 218-219°, whose

[1] T. Kubota and Y. Tomita, Chem. & Ind. 230 (1958).

[2] T. Kariyone et al., J. Pharm. Soc. Japan 47, 133 (1927); 49, 702 (1929).

mixed m.p. and I.R. spectrum showed the identity of (XI) with the semicarbazone of natural erythrocentaurin (I).



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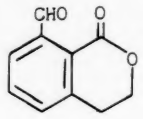

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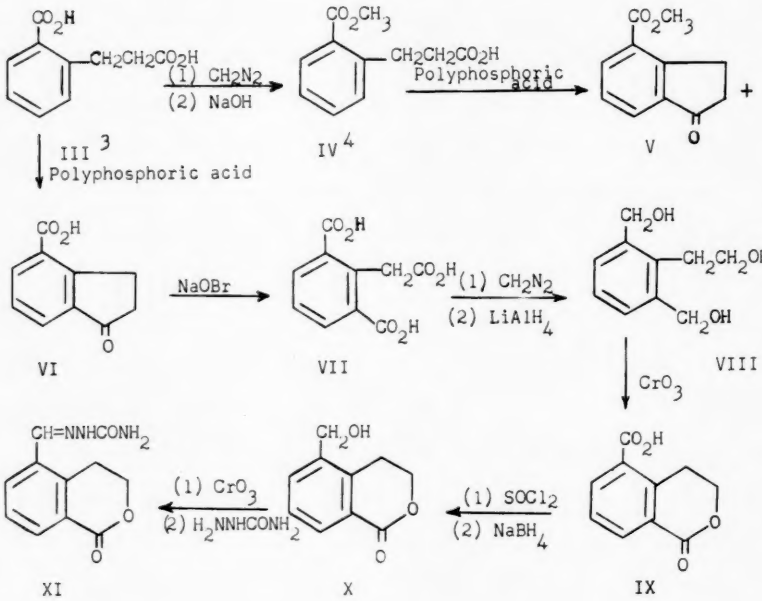

The alternative lactone formula IXa of the reaction product of the triol VIII was eliminated by the following evidence (I) Methylation of XVI followed by lithium aluminum hydride reduction yielded XVII which, on chromic

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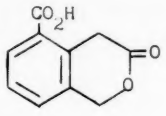
[3] Organic Syntheses 34, 8 (1954)

[4] S. Murahashi and R. Anzai, Chem. High Polymers 3, 33 (1946).

acid oxidation, gave the lactone XV, analogous to the lactone IX, whose structure was confirmed by a sequence of reactions, XII to XV. (2) The infra-red band (5.82μ) of IX is in agreement with the structure of an aryl-conjugated δ-lactone, such as gentinine (5.82μ)[5] and XV (5.87μ). (XIII): $C_{10}H_{10}O_2$, m.p. 109-110° (Found: C, 74.56; H, 6.22. Calc.: C, 74.05; H, 6.22). (XIV): $C_{10}H_{10}O_3$, m.p. 151-152° (Found: 67.46; H, 5.68. Calc.: C, 67.40; H, 5.66) (XV): $C_{10}H_{10}O_2$, m.p. 72-73° (Found: 74.25; H, 6.36. Calc.: 74.05; H, 6.22). (XVI): $C_{10}H_{10}O_4$, m.p. 184-185° (Found: C, 61.76; H, 5.22 Calc.: 61.85; H, 5.19).



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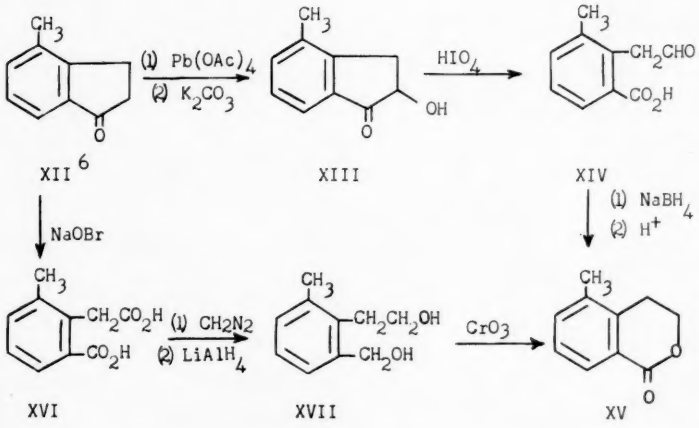

[5] T.R. Govindachari et al., J.Chem.Soc. 551 (1957).

[6] R.N. Chakravarti, J. Indian Chem.Soc. 20, 393 (1943).

Tetrahedron Letters No. 6, pp. 226-229, 1961. Pergamon Press, Inc. Printed in the United States of America.

1961

DETERMINATION OF THE ABSOLUTE CONFIGURATION OF JATAMANSONE (VALERANONE) BY THE AXIAL α-HALOKETONE RULE[1]

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and

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(Received 23 March 1961)

THE skeletal structure[2,3] of jatamansone (identical with valeranone[4]) is unique among sesquiterpenes. By establishing the location[2b,5] of the carbonyl group, the constitutional problem can be considered to be settled completely in terms of structures I - IV, the only question remaining being the stereochemistry of this sesquiterpene. The degradation[2b] of jatamansone to (-)-carvomenthone (V) fixes the absolute configuration of the carbon atom to which the isopropyl group is attached, thus leaving the four isomeric representations I - IV open for further consideration. We

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[1] Optical Rotatory Dispersion Studies LII. For preceding paper see C. Djerassi, E. Lund, E. Bunnenberg and J.C. Sheehan, J.Org.Chem. In press.

[2] (a) T.R. Govindachari, B.R. Pai, K.K. Purushothaman and S. Rajadurai, Tetrahedron Letters No. 15, 5 (1959); (b) Chem. & Ind. 1059 (1960).

[3] J. Krepinsky, M. Romanuk, V. Herout and F. Sorm, Tetrahedron Letters No. 7, 11 (1960)

[4] J. Krepinsky, V. Herout and F. Sorm, Tetrahedron Letters No. 3, 9 (1960).

[5] T.R. Govindachari, B.R. Pai, K.K. Purushothaman and S. Rajadurai, Tetrahedron 12, 105 (1961).

should now like to report a unique solution to this problem by means of optical rotatory dispersion[6] measurements.

The axial α-haloketone rule[7] permits the predication of the sign of the Cotton effect in a cyclohexanone which contains an axial bromine (chlorine or iodine) atom in the α-position. The effect of the axial halogen atom is so strong as to override[8] the rotational contributions of all other substituents in the molecule and these can, therefore, be ignored. Dibromojatamansone (VI)[2a,5] represents an excellent substrate for application of the axial α-haloketone rule[7] as the location of the bromine atoms is known and the axial character could be established by ultraviolet spectroscopic means (λ_{max} 305 mμ, log ε 3.03 vs. 285 mμ, log ε 1.80 for jatamansone).

The ring fusion of jatamansone can be either trans (I,II) or cis (III, IV). While the conformational situation in cis-decalones is usually complicated by the fact that two all-chair conformations need to be considered, this problem does not exist here since the absolute configuration of the isopropyl-bearing carbon atom is known. Consequently, we need to consider only that cis-decalone conformation where the isopropyl group occupies the equatorial orientation.

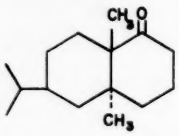
In the trans series, it is likely that in II the non-bonded 1,3-interaction between the axial isopropyl and methyl substituents forces the non-oxygenated ring into a boat-like conformation, but this should not affect the prediction of the sign of the Cotton effect based on the axial

[6] C. Djerassi, Optical Rotatory Dispersion. McGraw-Hill, New York (1960).

[7] C. Djerassi and W. Klyne, J. Amer. Chem. Soc. 79, 1506 (1957) and chapter 9 in ref. 6.

[8] C. Djerassi, Tetrahedron In press.

α-haloketone rule, since we need be concerned only with the conformation of the bromine-containing ring.



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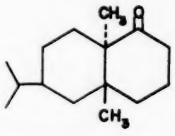

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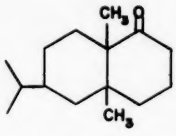

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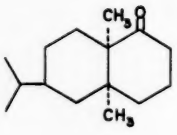

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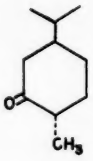

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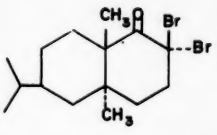

VI

If we now consider the dibromo derivatives of the four possible jetamansone representations I-IV in the light of the axial α-haloketone rule, it will be seen that only the dibromo ketone VI, derived from expression I, will exhibit a positive Cotton effect, while the dibromo ketones of II, III and IV would possess a negative Cotton effect. These predictions are based on the reasonable assumption (judging by inspection of Dreiding models) that the oxygenated ring will remain in a chair-like conformation in I-IV after bromination.

Experimentally, there was observed a positive Cotton effect in dioxane solution ($[\alpha]_{350}^{peak}$ + 777°)[9], whereupon it follows that jatamansone is correctly represented by stereoformula I. This, in turn, implies that,

[9] The position of the peak occurs at a wavelength which is higher than that noted usually for axial α-bromoketones (C. Djerassi, J. Osiecki, R. Riniker and B. Riniker, J. Amer. Chem. Soc. 80, 1216 (1958) but H.P. Sigg and C. Tamm (Helv. Chim. Acta 43, 1402 (1960)) have recently encountered several α,α-dibromoketones whose rotatory dispersion extrema were displaced to the same extent.

if jatamansone arises biogenetically by methyl migration from an eudalenoid precursor, the latter must possess the opposite absolute configuration from that of the usual eudesmol type of sesquiterpene.[10] It is noteworthy that the presently described stereochemical assignment represents an instance where application of the axial α-haloketone rule served to settle the nature of the ring fusion (trans or cis) as well as the absolute configuration of the centers involved in that ring fusion.

[10] R. Riniker, J. Kalvoda, D. Arigoni, A. Fürst, O. Jeger, A.M. Gold and R.B. Woodward, J. Amer. Chem. Soc. 76, 313 (1954).

Tetrahedron Letters No.7, pp. 231-233, 1961. Pergamon Press Inc. Printed in the United States of America.

961

THE TOTAL SYNTHESIS OF PHYLLOCLADENE

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Houston, Texas

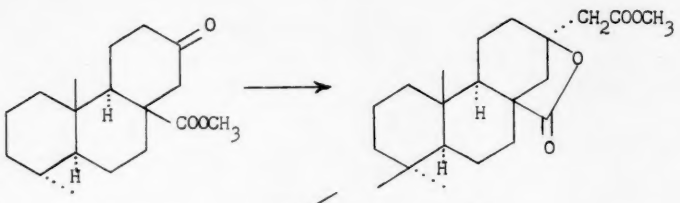
(Received 28 March 1961)

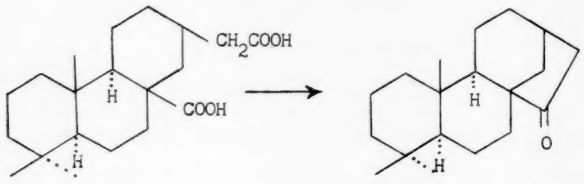
THE total synthesis of the optically active keto ester (I), a known degradation product of phyllocladene, was recently reported from this laboratory.[1] We wish at this time to record the total synthesis of phyllocladene itself.

Treatment of I with zinc and methyl bromoacetate according to the Reformatsky procedure affords the lactonic ester (II), m.p. 133-134°, $[\alpha]_D^{22}$ + 17° (c, 1.00 chloroform), $\lambda_{max}^{CS_2}$ 5.63, 5.74 , (Found: C, 72.25; H, 9.08. $C_{21}H_{32}O_4$ requires: C, 72.37; H, 9.26), convertible by successive reaction with sodium methoxide, platinum-hydrogen and sodium hydroxide into the diacid (III), m.p. 204.5-205°, $[\alpha]_D^{26}$ + 7.2° (c, 0.70 chloroform), (Found: C, 71.20; H, 9.96. $C_{20}H_{32}O_4$ requires: C, 71.39; H, 9.59). Pyrolysis of III as the barium salt yields IV, m.p. 133.5-134°, $[\alpha]_D^{26}$ - 36° (c, 0.75 chloroform), $\lambda_{max}^{CS_2}$ 5.76 , which was shown by direct comparison to be identical with the corresponding ketone recently obtained from phyllocladene by Henderson and Hodges[2].

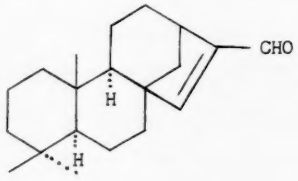
[1] R.B. Turner and P.E. Shaw, Tetrahedron Letters No.18, 24 (1960). See also R.F. Church, R.E. Ireland and J.A. Marshall, Ibid. No. 17, 1 (1960).

[2] R. Henderson and R. Hodges, Tetrahedron 11, 226 (1960).





Condensation of IV with ethyl formate in the presence of sodium hydride gave the expected hydroxymethylene ketone, which was converted, without purification, into the α, β-unsaturated aldehyde (V), m.p. 127-128°, $[\alpha]_D^{27}$ - 63.3° (c, 0.60 chloroform), $\lambda_{max}^{CS_2}$ 3.70, 5.96 , by reaction with butanone ethylene ketal - p-toluene-sulfonic acid, followed by treatment with lithium aluminum hydride and aqueous acid.[3] The identity of V with the product of this constitution derived by Briggs and his collaborators[4] from



V

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[3] cf. L. Ruzicka, C.F. Seidel, H. Schinz and M. Pfeiffer, Helv. Chim. Acta 31, 422 (1948).

[4] L.H. Briggs, B.F. Cain and B.R. Davis, Tetrahedron Letters No.17, 9 (1960).

isophyllocladene was established by direct comparison. The present synthesis, coupled with the conversion (Wolff-Kishner reduction) of V into phyllocladene,[4] constitutes a total synthesis of the latter compound.

It is a pleasure to acknowledge the support of the National Institutes of Health and of the Robert A. Welch Foundation in the pursuit of this work.

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BIOGENESIS OF MACROLIDES.[1] ORIGIN OF THE BRANCHED METHYL GROUPS IN CLADINOSE AND MYCAROSE

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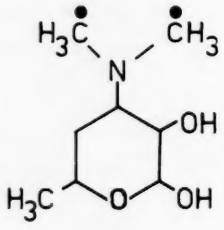
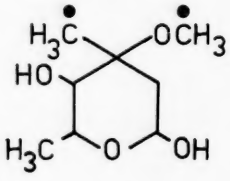
Chemisches Laboratorium der Universität Freiburg i.Br., Germany

(Received 22 March 1961)

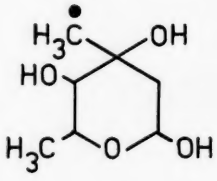
IN our investigation of the biogenesis of erythromycin[2] we had found that in an experiment with L-methionine-[methyl-^{14}C] the lactone ring was inactive, while desosamine (I)[3] contained about 1/3 and cladinose (II)[4] about 2/3 of the activity, even though II has only one O-methyl group while desosamine has a dimethylamino group. As one explanation for this result we assumed that methionine might supply not only the methoxyl group in II but also the C-methyl group at C-3. We now wish to report the experimental proof that the C-methyl groups at C-3 in cladinose and mycarose



I



II



III

• denotes origin from the methyl group of methionine

[1] Part III: H. Grisebach and H. Achenbach, Z. Naturf. In press.

[2] H. Grisebach, H. Achenbach and W. Hofheinz, Z. Naturf. 15b,560 (1960).

[3] E.H. Flynn, M.V. Sigal, Jr., P.F. Wiley and K. Gerzon, J.Amer. Chem. Soc. 76, 3121 (1954).

(III)[5] originate from the methyl group of methionine.

Fermentation of Streptomyces erythreus and Streptomyces halstedii in the presence of L-methionine-[methyl-^{14}C] yielded radioactive erythromycin and magnamycin (IV)[6] respectively. The distribution of the radioactivity is shown in Table 1.

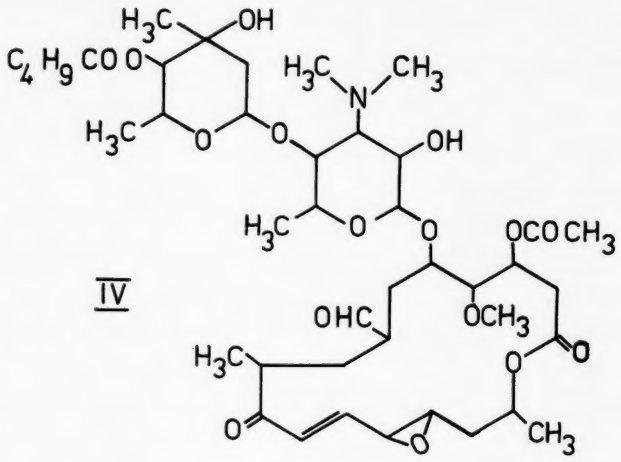
Table 1

Compound	Per cent radioactivity
Erythromycin	100
Desosamine	40
Cladinose	60
Dimethylamine from desosamine	100 (of desosamine)
Acetic acid from Kuhn-Roth oxydation of cladinose	67 (of cladinose)
Carboxyl group of acetic acid	0.7
Magnamycin	100
Carimbose	79
Isovaleric acid	0
Acetic acid from Kuhn-Roth oxydation of carimbose	0.4
Acetic acid from Kuhn-Roth oxydation of magnamycin	24
Mycarose	23
Acetaldehyde from periodate oxydation of mycarose	0

[4] P. F. Wiley and O. Weaver, J.Amer.Chem.Soc. 78, 808 (1956)

[5] P.P. Regna, F.A. Hochstein, R.L. Wagner, Jr. and R.B. Woodward, J.Amer.Chem.Soc. 75, 4625 (1953).

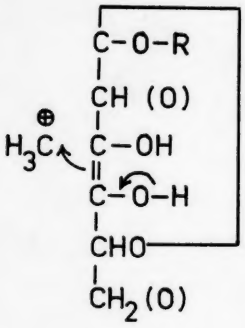
[6] R.B. Woodward, Angew. Chem. 69, 50 (1957).



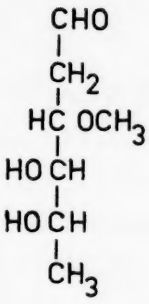
IV

In agreement with our previous results[2] cladinose contained 60 per cent and desosamine 40 per cent of the total activity in erythromycin. Sixty-seven per cent of the activity in cladinose was in the C-methyl groups, while the entire activity in desosamine was localized in the dimethylamino group. In the case of magnamycin no activity was found in the C-methyl groups of carimbose (magnamycin minus isovaleryl-mycaroside). The activity in carimbose is probably distributed between the N-dimethylamino group of mycaminose and the methoxyl group on the lactone ring; the branched methyl group at C-10 is derived from propionate.[1] The entire activity in mycarose was localized in the C-methyl groups. Periodate oxidation of III yielded acetaldehyde (C-5 and C-6) which was inactive, thus proving that only the methyl group at C-3 originated from methionine. This almost certainly applies to cladinose as well.

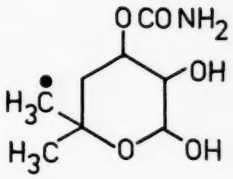
The selective methylation of the sugar carbon chain at C-3 seems reasonable only if it is assumed that it occurs at an intermediate stage in which C-3 is activated. A suitable activated intermediate would be, for instance, a uridinediphosphate derivative of V.



V



VI



VII

The origin of the unbranched carbon chain of cladinose and mycarose is currently being investigated in this laboratory. It seems plausible that these sugars are biogenetically very closely related to L-oleandrose (VI)[7] from oleandomycin and oleandrin. Possibly the steric configuration of II and III, as yet unknown, is the same as that of VI.

Birch et al.[8] have recently demonstrated that in the case of novobiose (VII) from novobiocin one of the two terminal C-methyl groups also originates from methionine.

Acknowledgements: We gratefully acknowledge the support of our work by the Deutsche Forschungsgemeinschaft.

We are indebted to Professor R.B. Woodward and to Dr. F.A. Hochstein (Pfizer Co., Groton, Conn.) for generous samples of magnamycin and its degradation products as well as for details of experimental procedures. We thank the Eli Lilly Co., Indianapolis, for erythromycin and Drs. K. Gerzon and P. Wiley for samples of desosamine and cladinose. Cultures of Streptomyces halstedii were kindly furnished by the U.S. Department of Agriculture, Peoria.

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[7] H. Eis, W.D. Celmer and K. Murai, J.Amer.Chem.Soc. 80, 3777 (1958).

[8] A.J. Birch, D.W. Cameron, P.W. Holloway and R.W. Rickards, Tetrahedron Letters No. 25, 26 (1960).

Tetrahedron Letters No.7, pp. 238-242, 1961. Pergamon Press, Inc. Printed in the United States of America.

AMIDATION AND AMINOALKYLATION OF OLEFINS: BLOCKING TECHNIQUES IN RADICAL CHAIN REACTIONS

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(Received 23 March 1961)

METHYL formate reacts with olefins in the presence of t-butyl peroxide to give 1:1 adducts and large proportions of higher telomeric methyl esters.[1] Olefins also add to amines by homolytic processes to form telomers derived by substitution of alkyl groups for hydrogen alpha to the amine group.[2] It is now reported that dimethylformamide and olefins react (equation 1) in the presence of initiators to give mixtures of isomeric adducts: N,N-dimethyl

$$RCH{=}CH_2 + H\text{-}CO\text{-}N(CH_3)_2 \rightarrow \begin{cases} RCH_2CH_2CON(CH_3)_2 & I \\ R(CH_2)_3N(CH_3)CHO & II \end{cases} \qquad (1)$$

amides (I, amidation) and N-alkyl-N-methylformamides (II, aminoalkylation) along with the corresponding higher telomers. The radical chain processes thus involve competitive transfer from dimethylformamide of hydrogen which

[1] W.H. Urry and E.S. Huyser, J.Amer.Chem.Soc. 75, 4876 (1953). Similar reactions of ethyl formate and ethylene yield mixtures of ethyl esters of telomeric acids, $H\text{-}(CH_2CH_2)_x\text{-}CO_2C_2H_5$, and formate esters of telomeric secondary alcohols.

[2] W.H. Urry and O.O. Juveland, J.Amer.Chem.Soc. 80, 3322 (1958).

is adjacent to carbonyl or on a carbon attached to nitrogen. The adducts are hydrolyzed readily to carboxylic acids and N-alkyl-N-methylamines. The overall sequence of addition and hydrolysis thus serves as an effective joint method for carboxylating and aminoalkylating olefins.

A selective method of amidation results from reaction of t-butylformamide and olefins in the presence of initiators. Addition occurs efficiently (equation 2) to give N-t-butyl amides (III) and corresponding higher telomers.

$$(RCH{=}CH_2 + H\text{-}CO\text{-}NH\text{-}C(CH_3)_3 \longrightarrow \underset{\text{III}}{RCH_2CH_2CONH\text{-}C(CH_3)_3} \qquad (2)$$

By the blocking inherent in the t-butyl group in t-butylformamide, transfer of hydrogen is restricted to that adjacent to the carbonyl group. t-Butylformamide is also of advantage over dimethylformamide in that the yields of higher telomers are considerably smaller. Since N-t-butyl amides (III) may be hydrolyzed under appropriate conditions, a general method is available for converting olefins to higher carboxylic acids.

Selective homolytic aminoalkylation of olefins is obtained in reactions with N,N-dimethylacetamide (equation 3) and with N-methylacetamide (equation 4). The products are N-alkyl-N-methylacetamides (IV)

$$RCH{=}CH_2 + (CH_3)_2NCOCH_3 \longrightarrow RCH_2CH_2CH_2N(CH_3)COCH_3 \qquad (3)$$

$$RCH{=}CH_2 + CH_3NHCOCH_3 \longrightarrow RCH_2CH_2CH_2NHCOCH_3 \qquad (4)$$

and N-alkylacetamides (V), respectively, and their corresponding higher telomers. N,N-Dimethylacetamide and N-methylacetamide display blocking specificities in that hydrogen on carbon attached to nitrogen is transferred rather than that on carbon adjacent to carbonyl. Since the amides, (IV) and (V), are convertible to N-alkylmethylamines and alkylamines, the combination of selective addition and hydrolysis serves as a simple method for aminoalkylating olefins.

General experimental methods and additional theoretical features are illustrated in the following examples. Dropwise addition (16 hr) of 1-octene

(1.0 mole) and t-butyl peroxide (0.05 mole) to dimethylformamide (30 moles) at 132° and subsequent reaction (18 hr) results in 87% conversion of 1-octene to a 60:40 mixture[3] of the 1:1 telomers [b.p. 91° (0.5 mm), n_D^{20} 1.4519, 56% yield] : N,N-dimethylnonanamide (VI) and N-methyl-N-nonylformamide (VII).[4,5] Reaction of 1-octene (1.0 mole), dimethylformamide (30 miles) and t-butyl peroxide (0.02 mole; atm press, 130-133°, 43 hr) during which additional initiator was added after 8 hr (0.02 mole), 20 hr (0.02 mole) and 36 hr (0.005 mole) gave VI and VII (47%), 2:1 telomers (21%) and crude 3:1 telomers (12%).[6] The composition and yield of the mixture of VI and VII were not significantly altered by initiating the additions with t-butyl peroxide or cumyl peroxide over the range, 115-150°. The preparative results thus indicate that the energies involved in formation of the $(CH_3)_2N\dot{C}=O$ and $\cdot CH_2N(CH_3)CHO$ radicals are similar. In the absence of olefins, dimethylformamide (8.2 moles) is converted by t-butyl peroxide (0.55 mole) at 132° (65% yield) to N,N,N',N'-tetramethyloxamide (6.0%), N,N'-diformyl-N,N'-dimethylethylenediamine (72%) and N-formyl-N-methylaminoacetic acid dimethyl amide (22 %); these results are comparable to those recently reported.[7]

[3] All new products gave satisfactory analyses.

[4] Other products are (1) 2:1 telomers (23%): N,N-dimethyl 3-n-hexyl-undecanamide and N-methyl-N-1-(3-n-hexylundecyl) for mamide [b.p. 153° (0.2 mm)], and (2) 3:1 adducts [12%, b.p. 197-200°(0.3 mm)].

[5] Hydrolysis of the mixture of VI and VII was effected quantitatively to nonanoic acid and N-methylnonylamine in refluxing hydrochloric acid.

[6] Addition of dimethylformamide to 1-decene and methyl 10-undecylenate also occurred satisfactorily.

[7] K. Schwetlick, Angew. Chem. 72, 208 (1960)

t-Butylformamide[8] was added to methyl 10-undecylenate and 1-octene. Reaction of methyl 10-undecylenate (0.57 mole), t-butylformamide (17.8 moles), and t-butyl peroxide (0.041 mole; 24 hr, 130°) gave methyl 11- (t-butylcarbamoyl) undecanoate[3] [VIII, 61% yield, m.p. 41-43°, b.p. 177-180°(0.8 mm.)] and higher-boiling products (41 g). Similarly 1-octene (0.67 mole), t-butylformamide (19.2 moles) and t-butyl peroxide (0.044 mole) yielded N-t-butylnonanamide[3] (IX, 77% yield, b.p. 115° (1 mm), n_D^{20} 1.4492) and higher telomers. Radical-dimerization of t-butylformamide (9.15 moles) by t-butyl peroxide (0.82 mole; 20 hr, 140°) also occurred to give N,N'-di-t-butyloxamide (73% yield, m.p. 181-182°).

Saponification of VIII to N-t-butyldodecanedioic acid amide[3] (X, m.p. 81.5-82.5°) was effected (97%) by minimal refluxing in aqueous-methanolic potassium hydroxide and acidification; hydrolysis of X in hot aqueous potassium hydroxide gave, after acidification, dodecanedioic acid (~100%). Dodecanedioic acid was obtained preparatively from VIII (0.088 mole) upon refluxing (6 hr) with stirred potassium hydroxide (0.55 mole), water (5 ml), diethylene glycol (15 ml) and butyl Cellosolve[9] (100 ml), dilution with water, separation, and acidification. A similar procedure resulted in effective hydrolysis of IX to nonanoic acid and t-butylamine.

Selective amidation of 1-octene was obtained with N,N-dimethylacetamide and N-methylacetamide, respectively. Reaction of N,N-dimethylacetamide (21.8 moles), 1-octene (0.67 mole), and t-butyl peroxide (0.027 mole; 72 hr, 125°) yielded N-methyl-N-nonylacetamide[3] (XII, 39% yield, 81% conversion

[8] Prepared by adding t-butylamine (25 moles) to cooled 90% formic acid (47 moles), distillation until the mixture reaches 175°, storing the residue over potassium carbonate, filtering, and distilling: 90% yield, b.p. 82° (10 mm), n_D^{20} 1.4340.

[9] Acidic hydrolyses were unsatisfactory.

of 1-octene, b.p. 120-122° (1 mm), n_D^{20} 1.4535) along with higher telomers. Similarly N-methylacetamide (7.2 moles), 1-octene (0.24 mole) and t-butyl peroxide (0.0165 mole; 128°, 42 hr) gave N-nonylacetamide [XIII, 33% yield, 90% conversion of 1-octene, b.p. 143-145° (1.5 mm), m.p. 34-35°] and higher telomers.[10] Radical-dimerizations of N,N-dimethylacetamide (12 moles) and N-methylacetamide (12 moles), respectively, by t-butyl peroxide (1 mole; 22 hr, 140°) occurred to yield N,N'-diacetyl-N,N'-dimethylethylenediamine [85%, b.p. 155-160°(2 mm), m.p. 90-92°] and N,N'-diacetylethylenediamine (71%, m.p. 174-176°).

Hydrolysis of XII and XIII in refluxing hydrochloric acid occurs efficiently to give N-methylnonylamine and nonylamine, respectively.[11]

[10] Formamide and 1-alkenes are quite insoluble at 135°; however, addition occurs in the presence of t-butyl peroxide to give telomers of relatively high molecular weight.

[11] This research was initially sponsored by The Ohio State University Development Fund.

Tetrahedron Letters No. 7, pp. 243-248, 1961. Pergamon Press, Inc. Printed in the United States of America.

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THE TERTIARYBUTYLBENZENES

INTERMEDIATES IN THE PREPARATION OF

ORTHO-DI-TERTIARYBUTYLBENZENE

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(Received 6 March 1961)

SINCE the publications of Brown and co-workers[1], there has been considerable interest devoted to attempted syntheses of the unknown hydrocarbon o-di-t-butylbenzene.[2] The interest has been increased since the preparation by Hübel and Hoogzand[3] of 1,2,4-tri-t-butylbenzene. Bruson and co-workers[4] have already reported the preparation of o-phenylene-di-isobutyric acid (III) which presents an obvious route for the synthesis of o-di-t-butylbenzene. Recently we converted III into a derivative β,β'-di-hydroxy-o-di-t-butylbenzene (V). We now wish to report on some of the properties of this derivative of o-di-t-butylbenzene.

1,1,4,4-Tetramethyltetralone (I) was prepared according to Bruson and co-workers. The structure assigned to this compound was confirmed by its

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[1] H.C. Brown and K. LeRoi Nelson, J.Amer. Chem. Soc. 75, 24 (1953) ; H.C. Brown, D. Gintis and L. Domash, Ibid. 78, 5387 (1956).

[2] E. M. Arnett, J. Org. Chem. 25, 324 (1960) and references reported therein.

[3] W. Hübel and C. Hoogzand, Chem. Ber. 93, 103 (1960).

[4] H. A. Bruson, F.W. Grant and E. Bobko, J. Amer. Chem. Soc. 80, 3633 (1958).

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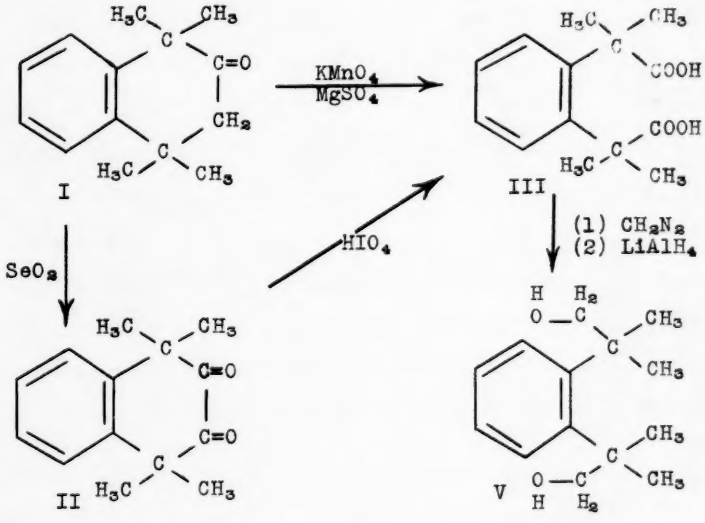
NMR spectrum. This spectrum clearly showed the four C-methyl groupings. A peak at 8.69 (p.p.m. relative to tetramethylsilane = 10) is attributed to the methyl groups on carbon 4, while the peak at 8.56 is attributed to the methyl groups on carbon 1. The shift is due to the adjacent carbonyl function in the latter case. The two methylene hydrogens appear at 7.36 and the four aromatic hydrogens at 2.74. This compound showed a strong band in the infra-red at 749 cm^{-1} (CS_2) attributed to ortho-di-substitution and carbonyl absorption at 1700 cm^{-1}. The ultra-violet spectrum (Fig. 1) showed two peaks at λ_{max} 264 mμ, ε 281 and λ_{max} 271 mμ, ε 242 (cyclohexane).

The tetralone I (m.p. 74-75°) was oxidized by potassium permanganate according to the procedure of Bruson[4] to produce a di-carboxylic acid which, after repeated recrystallizations, had a m.p. 218-219°. (Found: C, 67.03, 67.15; H, 7.32, 7.32. Calc. for $C_{14}H_{18}O_4$: C, 67.16; H, 7.25.) On the other hand, Bruson reported a melting point of 181-183° for this acid. In order to establish the identity of our acid, an alternate synthesis was carried out. In this synthesis the tetralone I was oxidized with selenium dioxide to produce a yellow di-ketone (II) in 80% yield of m.p. 64-65°. (Found: Calc. for C, 77.85, 77.85; H, 7.57, 7.62; O, 14.89, 14.80. $C_{14}H_{16}O_2$: C, 77.74; H, 7.46; O, 14.80%) This compound showed carbonyl absorption in the infra-red at 1690 cm^{-1} and also a strong band at 748 cm^{-1}. The ultra-violet spectrum showed bands at λ_{max} 264 mμ, and 271.5 mμ. This di-ketone was oxidized by periodic acid to produce the acid III which proved identical by mixed melting points and spectra to the acid obtained by direct oxidation of I with permanganate. The periodate oxidation of the diketone produced a high yield of the pure acid (III) whereas permanganate oxidation of I yielded an impure product melting as low as 185° before repeated recrystallizations. This probably explains the discrepancy between the melting point of III reported in the literature[4] and that of the pure acid. The acid (III) was converted to an anhydride

in 87% yield by refluxing in excess acetic anhydride. The anhydride, o-phenylene-di-isobutyric anhydride, showed carbonyl absorption at 1770 and 1725 cm^{-1} and a band at 756 cm^{-1} indicated ortho-di-substitution. The acid was converted into its corresponding ester di-methyl-o-phenylene-di-isobutyrate (IV) in 92% yield with diazomethane. The purified ester had m.p. 102-103°. (Found: C, 69.33; H, 8.01; O, 23.39. Calc. for $C_{16}H_{22}O_4$: C, 69.03; H, 7.97; O, 23.00%) The ultra-violet spectrum showed a single broad band at 264 mμ, ε 252 and the infra-red spectra showed carbonyl absorption at 1720 cm^{-1}. The NMR spectrum showed the four C-methyl groups at 8.40 and the two O-methyls at 6.39, while the four aromatic hydrogens appeared at 2.73.

The di-ester (IV) was reduced with lithium aluminium hydride to give a 95% yield of the corresponding diol β,β'-di-hydroxy-o-di-t-butylbenzene (V) m.p. 115-116°. (Found: C, 75.34; H, 9.98; O, 15.12. Calc. for $C_{14}H_{22}O_2$: C, 75.63; H, 9.98; O, 14.39%). The infra-red spectrum of this compound lacked carbonyl absorption. In a KBR pellet the compound showed



broad hydroxyl absorption at 3350 cm^{-1}. A strong band at 1037 was attributed to the $-CH_2OH$ groups and a strong band at 750 cm^{-1} to ortho-di-substitution. In chloroform solution, the compound showed hydroxyl bands at 3400 and 3570 cm^{-1}. The ultra-violet spectrum (Fig. 1) showed a single band at λ_{max} 265 mμ, ε 225 and the fine structure exhibited by the tetralone (I) is absent in the diol. The relationships between these compounds are illustrated on p. 245.

The ortho-tertiarybutyl groups in the diol (V) apparently have not resulted in serious strain or distortion of the benzenoid ring, since such strain is known to cause a bathochromic shift in the ultra-violet spectra with increased intensity,[5,6] while the opposite has been observed for compound (V). A further clue to the unusual effects of the ortho-groupings in V is obtained from its NMR spectrum (Fig. 2). This spectrum shows a peak at 8.51 for C-methyls of intensity corresponding to the four groups. A peak at 8.21 corresponds to two hydroxyl hydrogens and the peak at 6.22 to the four methylene hydrogens. The absorption in the region for aromatic protons is now split into two groups of bands of approximately equal weights and corresponding to the total of four hydrogens. A detailed interpretation of this NMR spectrum is not offered at this time but an expedient suggestion would be that the peaks due to the hydrogens ortho to the bulky groupings have been shifted and are represented by the bands near 2.55, whereas the bands near 2.78 represent the other (meta) hydrogens. It is to be noted that the aromatic hydrogens in compounds (I) and (IV) absorb near this region of 2.78. It may well be that the two ortho hydrogens interact strongly through association with hydroxyl oxygens (see structure V) to account for the observed splittings. Such an interaction

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[5] M.P. Cava, A.A. Deana and K. Muth, J. Amer. Chem. Soc. 82, 2524 (1960).

[6] M. Ballester and J. Castaner, J. Amer. Chem. Soc. 82, 4259 (1960).

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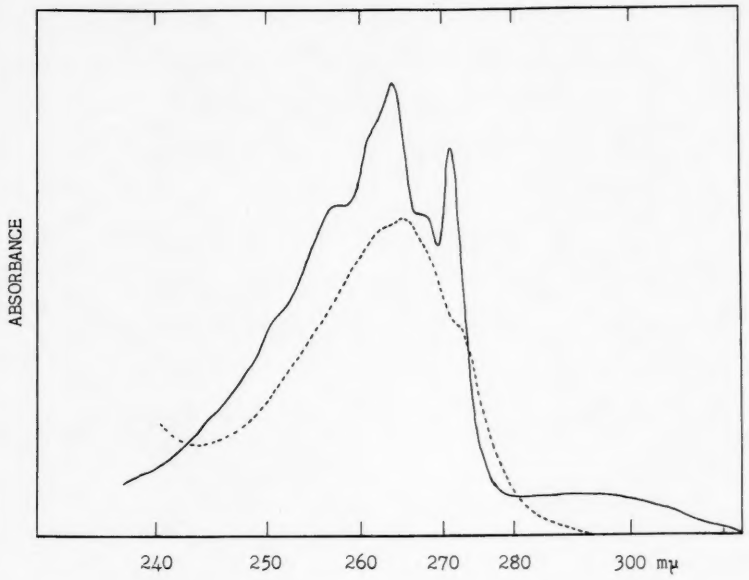

FIG. 1. Ultra-violet spectra.
——— 1,1,4,4-tetramethyltetralone (I);
- - - - β,β-di-hydroxy-o-di-t-butylbenzene (V).

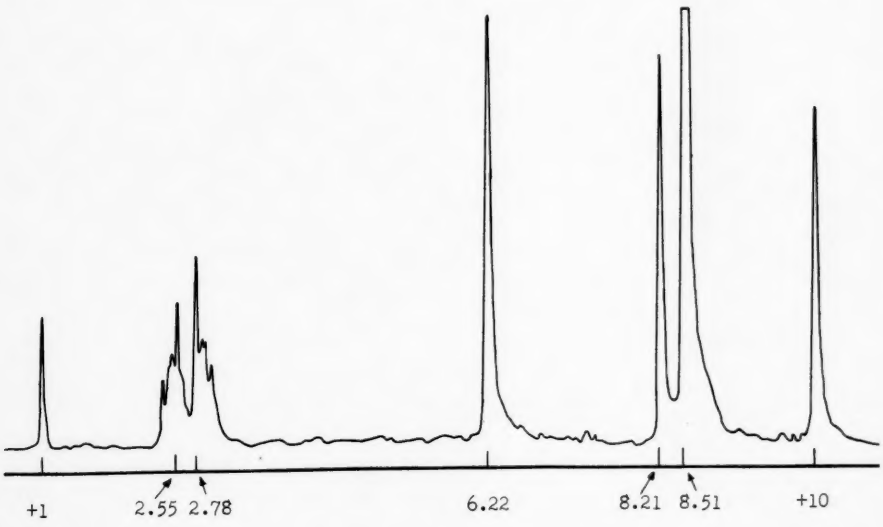

FIG. 2. NMR spectrum (V).

might also account for the ultra-violet spectrum of this compound.

A Stuart-Briegleb model was constructed of V and it was noted in this model that the CH_2OH groupings would probably swing away from each other to permit the two t-butyl groupings to be ortho on the ring; and, if such is the case, the two oxygen atoms would interact very strongly with the ortho-situated hydrogens. It is conceivable that this association is sufficiently strong to relieve some of the strain expected in this system. Further experiments are continuing on these compounds and will be reported on at a later date.

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REGARDING PROTONATED CARBONYL DERIVATIVES AND THEIR CONJUGATIVE ACCEPTOR CAPACITIES

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(Received 16 March 1961)

WE report herein results which are pertinent to three matters of current interest: the relative conjugative charge-accepting capacities of protonated and unprotonated carbonyl compounds,[1] the question of the preferred site of protonation of amides,[1,2] and the correlation of NMR and reactivity parameters.[3]

Currently the most discriminate measure available of the order of conjugative charge release and withdrawal by substituent groups in ground state molecules is the fluorine atom mesomeric charge perturbation (m.c.p.) due to m- and p-substituents in fluorobenzenes.[3] As previously defined:[4] m.c.p. = $-(\delta^F_p - \delta^F_m)$, where δ^F_m refers to the F^{19} NMR shielding parameter of a meta-substituted fluorobenzene and δ^F_p refers to that for the corresponding para isomer.

For uncharged +R substituents enhanced positive m.c.p. values have been

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[1] (a) R. Stewart and K. Yates, J.Amer.Chem.Soc. 80, 6355 (1958); 82, 4059 (1960)
(b) K. Yates and R. Stewart, Canad. J. Chem. 37, 664 (1959);
(c) J.T. Edward, H.S. Chang, K. Yates and R. Stewart, Ibid. 38, 1518 (1960)

[2] G. Fraenkel and C. Franconi, J. Amer. Chem. Soc. 82, 4478 (1960) and references given therein.

attributed to the interaction represented by:[3,4]

I

Since the interaction structure (I) involves a relatively long-range charge separation, it is of interest to have information concerning the relative importance of such an interaction structure and the analogous interaction structure (II), which involves charge re-distribution; e.g.

II

We have measured m.c.p. values directly in very dilute 99.8% H_2SO_4 solutions containing m-substituted fluorobenzene and its p-isomer, the substituent in each case corresponding to the general formula COX (X's are as listed in Table I). Under these conditions, it is known that for all practical purposes each of the substituent groups is completely protonated.[1] Comparison of the m.c.p. values for corresponding protonated and unprotonated substituents (items 1 and 2 of Table I) indicates that charge withdrawal from fluorine is on the order of 3-fold greater for the former. Thus the expectation[5] that form (II) tends to make a substantially greater contribution to its resonance hybrid than does form (I) is confirmed. It is noteworthy, however, that the group X has a strong modulating influence on the acceptor capacity. Thus, the largest m.c.p. (greater downfield shift and electron withdrawal from F) for the uncharged COX substituents (COF) is only somewhat smaller than the smallest m.c.p. for a protonated substituent

[3] For recent review and earlier references, cf. R.W. Taft, Jr., J. Phys. Chem. 12, 1805 (1960).

[4] R.W. Taft, Jr. et al., J.Amer.Chem.Soc. 82, 756 (1960); cf. also H.S. Gutowsky et al., Ibid. 74, 4809 (1952).

[5] cf., for example, R.S. Mulliken, Tetrahedron 5, 256 (1959).

TABLE I. CORRELATION OF PROPERTIES OF ArCOX COMPOUNDS[a]

X	σ_R^o	σ_I	(1) M.c.p.(in p.p.m.) F-Ar-C(OH)X^+, 99.8% H_2SO_4 obs.[b]	calc.	(2) M.c.p.(in p.p.m.) F-Ar-COX, 75% aq. CH_3OH obs.	calc.	(3) ArY resonance effect,[3] Ioniz. CH_3O-⟨⟩-C(OH)X^+ $\log(K/K_o)-\sigma^o\rho$	calc.	(4) pK_a Values $C_6H_5C(OH)X^+$ obs.	calc.	(5) U.V.Absorption Max. $C_6H_5C(OH)X^+$, mμ obs.	calc.	(6) U.V.Absorption Max. C_6H_5COX, mμ obs.	calc.
O^-	-0.60[j]	-0.12[j]	6.6[c]	6.2	3.1[d]	2.7	-0.1	-0.1	+ 4.4	+ 4.2	235[e]	234	224[g]	223
NH_2	- .48	+ .10	13.2	13.8	4.6	5.3	- .2	- .4	- 2.2	- 1.9	245[e]	250	225[h]	230
OH	- .40	+ .25	19.5	18.8	6.6	7.0	- .5	- .6	- 7.3	- 7.1	260[f]	262	235[e]	234
OC_2H_5	- .41	+ .25	18.0	18.4	6.7	7.0	- -	- .6	- -	- 6.9	- -	260	- -	234
CH_3	- .10	- .05	27.5	28.4	7.3	7.5	-1.1	-1.1	- 6.2	- 5.3	290[f]	287	250[i]	248
H	.00	.00	33.9	33.2	9.0	8.7	-1.4	-1.3	- 7.1	- 8.0	296[f]	298	251[i]	253
F	- .34	+ .52	- -	24.3	10.1	9.5	- -	- .9	- -	-13.8	- -	270	- -	238
Equation:			$m.c.p.^+ = 42.8\sigma_R^o + 10.8\sigma_I + 33.2$		$m.c.p.^o = 8.5\sigma_R^o + 7.3\sigma_I + 8.7$		$\log(K/K_o) - \sigma^o\rho = -1.8\sigma_R^o - 0.4\sigma_I - 1.3$		$pK_a = -16\sigma_R^o - 22\sigma_I - 8.0$		$\lambda^+_{max.} = 104\sigma_R^o + 17\sigma_I + 298$		$\lambda^o_{max.} = 49\sigma_R^o + 4\sigma_I + 253$	
Correlation Coeff., R			0.994		0.944		0.985		0.947		0.989		0.972	

a. Items 3-6 are based upon data given in ref. 1.

b. M.c.p. values were obtained[4] in 99.8% H_2SO_4 solutions containing equimolar quantities of the m- and p- isomers at 10%, 7.5%, and 5% by volume of each and the results extrapolated linearly to 0%.

c. Data for the CO_2H group in 75% aq. CH_3OH.

d. Obtained in dilute 75% aq. CH_3OH containing excess base.

e. Obtained in 56-63% H_2SO_4.

f. Obtained in 95-99.5% H_2SO_4.

g. Obtained in 0.01 M NaOH.

h. Obtained in H_2O

i. Obtained in 44% H_2SO_4.

j. Obtained from F^{19} NMR shielding parameters for m- and p-fluorophenols in dilute 75% aq. CH_3OH containing excess base; cf. ref. 3.

$(COHNH_2^+)$; and, in general, among the m.c.p. values of Table I a nearly continuous gradient is apparent.

Recent NMR evidence indicates that O-protonation is substantially favored over N-protonation in aliphatic amides.[2] However, Stewart et al. have presented an argument favoring N-protonation of benzamide as the result of valuable basicity studies of substituted benzoyl derivatives.[1*] Their argument is based upon the observation that the pK_a 's of protonated p-substituted acetophenones, benzaldehydes and benzoic acids are better correlated by σ^+ that σ values, whereas the converse holds for protonated benzamides. The present results indicate that the observations of Stewart et al. are very likely not due to predominant N-protonation of the benzamides but rather result from the attenuating of conjugation between a -R para-substituent and the $C(OH)X^+$ group, produced by increasing conjugative charge-release from the group X.

We reach this conclusion through the fact that six chemical and physical properties (cf. Table I) are correlated to reasonable approximation (more precise correlations are not expected for several apparent reasons) for these systems by the equation:[6] $P=\sigma_I \rho_I + \sigma_R^\circ \rho_R$, where σ_I and σ_R° are substituent parameters[3] referring to the group X and ρ's are susceptibility parameters. These correlations demonstrate in a roughly quantitative way that increasing conjugative charge-release (corresponding to increasing negative values of σ_R°) from X decreases the effects resulting from resonance interaction between the carbonyl derivatives and the benzene (or substituted benzene) ring in a regular manner. If predominant O-protonation were not involved with the benzamides as well, these regularities would not be expected to hold.

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[6] R.W. Taft, Jr., J.Amer.Chem.Soc. 79, 1045 (1957); Ibid. 79, 5075 (1957). The wide variation of the ratio of the inductive and resonance blending coefficients, ρ_I and ρ_R, precludes adequate correlation of the data of Table I by any single substituent parameter equation.

*Note Added in Proof: cf., however, R.Stewart and L.J. Muenster, Canad. J.Chem. 39, 401 (1961).

Tetrahedron Letters No.7 pp.253-258, 1961. Pergamon Press, Inc. Printed in the United States of America.

THE SYNTHESIS AND REACTIONS OF SOME 1'-SUBSTITUTED 9,10-DIHYDRO-9,10-METHANOANTHRACENES[1]

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(Received 28 March 1961)

THE chemistry of 7-substituted bicyclo[2.2.1]heptanes (I) has been of considerable interest in recent years, particularly in connection with the behavior of the corresponding carbonium ions.[4] Aside from the saturated parent compounds, many unsaturated and aromatic variants have been prepared and studied.[4] An interesting group of compounds in this series which

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[1] The nomenclature used in the body of this Communication has been chosen to emphasize the close chemical relationship between compounds based on skeletons I and II. Thus, compounds II (b-j) will be referred to as 7-substituted dibenzobicyclo[2.2.1]heptadienes rather than the IUPAC indicated 1'-substituted 9,10-dihydro-9,10-methanoanthracenes.

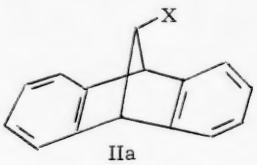
[2] Fellow of the Alfred P. Sloan Foundation.

[3] United States Rubber Co. Fellow, 1959-60.

[4] S. Winstein, M. Shatavsky, C. Norton and R. B. Woodward, J. Am. Chem. Soc. 77, 4183 (1955); S. Winstein and M. Shatavsky, ibid. 78,

has hitherto evaded synthesis[5] is represented by formula II (b-j), although the unsubstituted hydrocarbon, dibenzobicyclo[2.2.1]heptadiene, IIa, was prepared recently in an ingenious two-step synthesis devised by Vaughan and Yoshimine.[6] We wish to report the successful application of the

I



IIa
(X = H)

photochemical Wolff rearrangement to this synthetic problem, resulting in the conversion of an appropriately substituted dibenzobicyclo[2.2.2]octadiene into the desired 7-substituted dibenzobicyclo[2.2.1]heptadienes.

Treatment of the α-diketone III[5] with p-toluenesulfonylhydrazide in the usual manner[7] gave dibenzobicyclo[2.2.2]octadiene-2,3-dione

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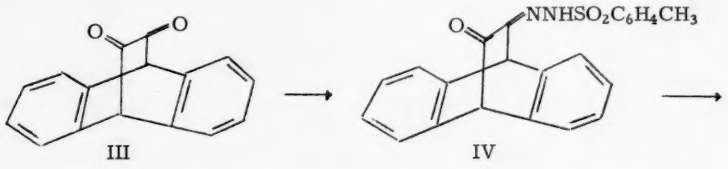
592 (1956); S. Winstein and E. T. Stafford, ibid. 79, 505 (1957); E. E. van Tamelen and C. I. Judd, ibid. 80, 6305 (1958); P. D. Bartlett and W. P. Giddings, ibid. 82, 1240 (1960); S. Winstein and C. Ordronneau, ibid. 82, 2084 (1960); P. R. Story, ibid. 82, 2085 (1960); P. R. Story and M. Saunders, ibid. 82, 6199 (1960); S. Winstein and R. L. Hansen, ibid. 82, 6206 (1960).

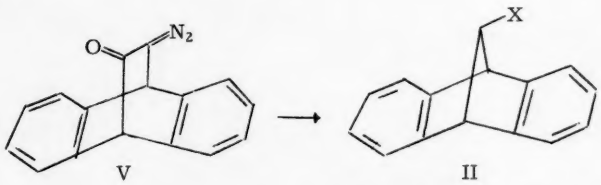
[5] W. R. Vaughan and M. Yoshimine, J. Org. Chem. 22, 528 (1957).

[6] W. R. Vaughan and M. Yoshimine, J. Org. Chem. 22, 7 (1957).

[7] M. P. Cava, R. L. Litle and D. R. Napier, J. Am. Chem. Soc. 80, 2257 (1958).

monotoluenesulfonylhydrazone (IV) (m.p. 195.5-196.5° (dec.); Found: C, 68.83; H, 4.54; N, 7.24; S, 8.01. $C_{23}H_{18}N_2O_3S$ requires: C, 68.63; H, 4.51; N, 6.96; S, 7.97%). Extraction with ether of a stirred suspension of IV in dilute, aqueous sodium hydroxide gave, in high yield, crystalline 3-diazodibenzobicyclo[2.2.2]octadien-2-one (V) (m.p. 149-151° (dec.); $\lambda\lambda_{max}^{KBr}$: 4.80, 5.99 μ; $\lambda\lambda_{max}^{EtOH}$ (log ε): 252 (4.06), 273 (3.75), 280 (3.80), 305 (3.60) mμ; Found: C, 77.58; H, 4.28; N, 11.44. $C_{16}H_{10}N_2O$ requires: C, 78.03; H, 4.09; N, 11.38%). Irradiation[8] of a solution of V in aqueous dioxane gave dibenzobicyclo[2.2.1]heptadiene-7-carboxylic acid (IIb) (m.p. 255-256°; $\lambda\lambda_{max}^{EtOH}$ (log ε): 253 (2.96)





b, X = CO_2H e, X = NCO h, X = $COCH_3$
c, X = COCl f, X = NH_2 i, X = $OCOCH_3$
d, X = CON_3 g X = OH j, X = $OSO_2C_6H_4Br$

[8] For a description of the apparatus see J. Meinwald and P. G. Gassman, J. Am. Chem. Soc. 82, 2857 (1960).

inflection, 272 (3.18), 279 (3.30) mμ; Found: C, 81.51; H, 5.25; molecular weight (Rast), 251. $C_{17}H_{12}O_2$ requires: C, 81.33; H, 5.12%; M.W., 236) in 16% yield.

Curtius degradation[9] of the acid IIb, via the acid chloride (IIc), the acid azide (IId), and the isocyanate (IIe), gave 7-dibenzobicyclo[2.2.1]-heptadienylamine (IIf) (m.p. 196-198° (dec.); $\lambda\lambda_{max}^{EtOH}$ (log ε): 254 (2.96) inflection, 272 (3.19), 278 (3.29) mμ; Found: C, 86.82; H, 6.11; N, 6.75. $C_{15}H_{13}N$ requires: C, 86.92; H, 6.32; N, 6.76%). Treatment of a cold solution of the amine IIf in dilute hydrochloric acid with sodium nitrite gave exclusively dibenzobicyclo[2.2.1]heptadien-7-ol (IIg) (m.p. 184-185°; $\lambda\lambda_{max}^{EtOH}$ (log ε): 254 (2.89) inflection, 272 (3.18), 278 (3.29) mμ; Found: C, 86.71; H, 5.96. $C_{15}H_{12}O$ requires: C, 86.51; H, 5.81%). The absence of any skeletal rearrangement in the course of the deamination is evident from the close similarity of the ultraviolet spectra of the alcohol and the amine. The structure of the alcohol, IIg, is supported by an independent synthesis as well as by oxidation to the 7-keto compound, VI, described below.

Methyl lithium reacted smoothly with acid IIb to give 7-acetyl-dibenzobicyclo[2.2.1]heptadiene (IIh) (m.p. 163-164°; Found: C, 86.78; H, 6.20. $C_{17}H_{14}O$ requires: C, 87.15; H, 6.02%). Baeyer-Villiger oxidation of IIh, followed by lithium aluminum hydride reduction of the

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[9] P. A. S. Smith in Organic Reactions, Vol. III, John Wiley and Sons, Inc., New York, N. Y., 1946, Chap. 9.

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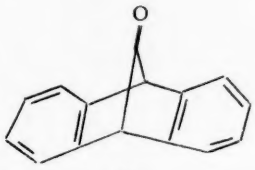
resultant acetate IIi (m.p. 164-164.5°; Found: C, 81.41; H, 5.82. $C_{17}H_{14}O_2$ requires: C, 81.58; H, 5.64%) gave IIg identical with that obtained via nitrous acid deamination of IIf. Acetolysis of the p-bromobenzenesulfonate IIj (m.p. 159-159.5°; Found: C, 58.59; H, 3.72; Br, 19.03; S, 7.50. $C_{21}H_{15}O_3BrS$ requires: C, 59.02; H, 3.54; Br, 18.70; S, 7.50%) also proceeded without rearrangement, giving the corresponding acetate, IIi, quantitatively. This solvolysis showed good first order kinetics, and gave a rate constant ($20.3 \pm 0.2 \times 10^{-6}$ sec.$^{-1}$ at 75.30 ± .02°) in accord with expectations, based on the data of Bartlett and Giddings.[4] Thus, it is unlikely that the carbonium ion derived from IIj derives any special benefit from the possibility of symmetrical charge distribution over both aromatic rings.

Oppenauer oxidation of IIg with aluminum isopropoxide and p-benzoquinone in benzene at room temperature for 3.5 days yielded anthracene, the product to be expected from decarbonylation of dibenzobicyclo[2.2.1]heptadien-7-one (VI).[10] When the reaction period was



VI

[10] Cf. the analogous result obtained by Bartlett and Giddings in the oxidation of anti-benzobicyclo[2.2.1]heptadien-7-ol.[4]

1961

shortened to 1 day, or when the oxidation was carried out using chromium trioxide in pyridine at 4° for 32 hours, the infrared spectrum of the crude reaction product contained a peak of medium intensity at 5.58 μ, characteristic of a 7-keto bridged system.[11] Chromatography of this crude oxidation product at 4° has given small amounts of a crystalline fraction (VI) with intense absorption at 5.58 μ.

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[11] The carbonyl absorption of the closely related benzobicyclo[2.2.1]-hepten-7-one is reported by Bartlett and Giddings[4] to occur at 5.58 μ.

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THE CONSTITUTION OF CEANOTHIC ACID, A RING-CONTRACTED TRITERPENOID

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(Received 3 April 1961)

CEANOTHIC acid was first isolated by Julian, Pikl and Dawson from Ceanothus americanus (Jersey Tea).[1] It was characterised as a hydroxy dicarboxylic acid and, further, it was reported that at the melting point it lost one molecule each of carbon dioxide and water.

Reinvestigation has required the revision of the empirical formula of ceanothic acid, m.p. 356-7°, $[\alpha]_D$ + 38° (in EtOH)[2] to $C_{30}H_{46}O_5$. The presence of a band in the infrared spectrum at 883 cm.$^{-1}$ together with the isolation of betulinic acid (I) (characterised by conversion to betulin diacetate and comparison with an authentic specimen) suggested that ceanothic acid belonged to the lupeol-betulin series of triterpenoids. This was confirmed when treatment with refluxing formic acid let to a monocarboxylic acid, $C_{30}H_{46}O_5$, m.p. 303-5°, $[\alpha]_D$ + 90°, in which the band at 883 cm.$^{-1}$ (attributed to the isopropenyl group) had disappeared and was replaced by a band at 1760 cm^{-1} attributed to a γ-lactone.[3]

The dehydration-decarboxylation reported[1], required that the hy-

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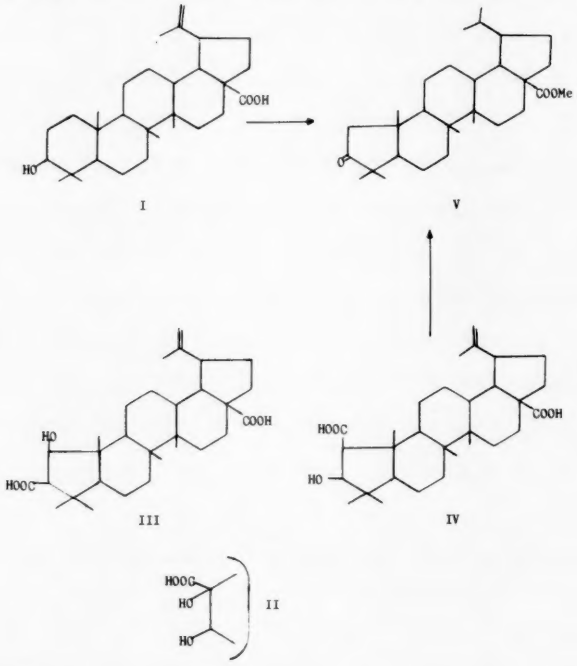
1 P.L. Julian, J. Pikl and R. Dawson, J. Amer. Chem. Soc. 60, 77 (1938).

2 Rotations were determined in chloroform unless otherwise stated. Melting points were determined on the Kofler block.

3 G.S. Davy, T.G. Halsall and E.R.H. Jones, J. Chem. Soc. 2696 (1951).

droxyl group be β to one of the carboxyl groups. This was confirmed as follows. Ceanothic acid dimethyl ester, m.p. 221-3°, $[\alpha]_D$ + 41° was converted into an oily benzoate which was pyrolysed to give, with loss of benzoic acid, the αβ-unsaturated ester, m.p. 166-8°, $[\alpha]_D$ - 16° which showed the expected absorption in the ultraviolet (λ_{inf} 215 mμ, ε7,500). The NMR spectrum[4] showed the presence of one vinyl hydrogen (τ = 3.9) as well as those bands (τ = 5.4, doublet) to be attributed to the isopropenyl group. The dehydration-decarboxylation product, which is not a lactone[1]



[4] The NMR spectra were determined in ca. 10% w v solution in CCl_4 using a Varian V-4302 spectrometer with TMS as internal standard.

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but an unsaturated acid, showed bands in the NMR spectrum indicative of two vinyl hydrogen atoms in addition to those due to the isopropenyl group. This required that both the hydroxyl group and the carboxyl be secondary, and this was confirmed by the NMR spectrum of ceanothic acid dimethyl ester itself which showed bands at τ = 5.98 and 7.51, attributed to methine hydrogen on carbon bearing oxygen and methine hydrogen α to carbonyl respectively.

Since no secondary carboxyl is possible in an unmodified lupeol-betulin type structure it seemed possible that the carboxyl group was produced, biogenetically, by a benzilic acid or acyloin type rearrangement. To contain the part structure -CH(OH)·CH(COOH)- would require the biogenetic precursor of ceanothic acid to have three contiguous carbon atoms all being methylene groups substituted by oxygen functions. This is possible in the lupeol-betulin system only in Ring A, whence (III) or (IV) follow for ceanothic acid.

Hydrogenation of ceanothic acid dimethyl ester in acetic acid solution (PtO_2) gave dihydroceanothic acid dimethyl ester, m.p. 262-3°, $[\alpha]_D$ + 21°. Oxidation (sodium dichromate-acetic acid) gave the corresponding ketone, m.p. 183-184°, $[\alpha]_D$ + 94°, ν_{max} 1750 cm^{-1}. Hydrolysis of this gave (with loss of carbon dioxide) (V) identical in every respect with an authentic specimen prepared from (I)[5], further characterised as the 2:4-dinitrophenylhydrazone, m.p. 161-163°. The ring contraction to give ceanothic acid (IV), though so far unique in the triterpenoid field, is biogenetically unexceptional and must occur, for instance,

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5 L. Ruzicka and O. Isler, Helv. Chim. Acta 19, 506 (1936); L. Ruzicka, M. Brenner, and E. Rey, 24, 515 (1941).

in the genesis of gibberellic acid. A similar ring contraction would accomodate the part structure (II) reported for senegenin.[6]

Acknowledgement. The authors are indebted to the National Research Council of Canada and to the Research Corporation for financial support, and wish to thank Dr. J.B. Stothers for the determination of the NMR spectra.

[6] M. Shamma and L.P. Reiff, Chem. and Ind. 1272 (1960).

Tetrahedron Letters No.8, pp. 263-266, 1961. Pergamon Press Ltd. Printed in Great Britain.

THE NATURE OF NEIGHBORING HYDROXYL GROUP ASSISTANCE IN THE ALKALINE HYDROLYSIS OF THE ESTER BOND

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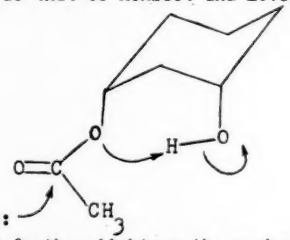
(Received 7 April 1961)

IT is now a well established fact that cis-cyclohexanediol monoacetates and (a,a) 1,3-cyclohexanediol monoacetates undergo alkaline hydrolysis with assistance of the neighboring hydroxyl group.[2-6] The mechanism suggested for the facilitation is that of Henbest and Lovell[2] (1).



(1)

In order to shed further light on the mechanism of facilitation we have determined the nature of the internal hydrogen bonding (in CCl_4 at high dilution; for methodology see refs. 2 and 7), as well as the hydrolytic

[1] Research Fellow, Department of Chemistry, Cornell Univ.

[2] H.B. Henbest and B.J. Lovell, J.Chem.Soc. 1965 (1957).

[3] S.M. Kupchan, W.S. Johnson and S. Rajagopalan, Tetrahedron 7, 47 (1959).

[4] S.M. Kupchan, and W.S. Johnson, J.Amer.Chem.Soc. 78, 3864 (1956).

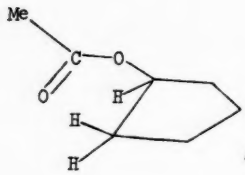
[5] S.M. Kupchan and C.R. Narayanan, J.Amer.Chem.Soc. 81, 1913 (1959).

[6] S.M. Kupchan, P. Slade and R.J. Young, Tetrahedron Letters No.24,22 (1960).

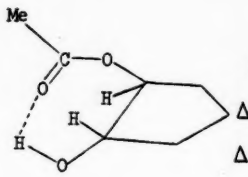
[7] R. West, J.J. Korst and W.S. Johnson, J.Org.Chem. 25, 1976 (1960).

Hydrolysis In H_2O at 78° (μ=1.0M; k_r relative)

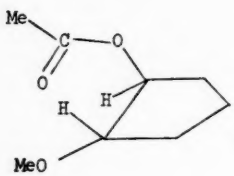
Dotted lines show hydrogen bond



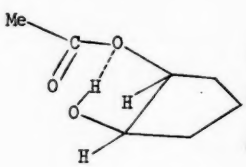
k_r 1.0
$\Delta H^{\ddagger}$ 11.3
$\Delta S^{\ddagger}$ -31.6



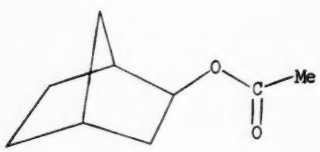
k_r 21.4
$\Delta H^{\ddagger}$ 15.3
$\Delta S^{\ddagger}$ -14.2



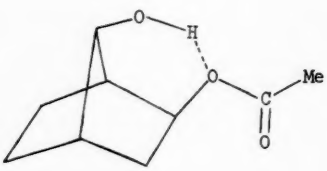
k_r 3.2
$\Delta H^{\ddagger}$ 11.9
$\Delta S^{\ddagger}$ -27.6



k_r 47.3
$\Delta H^{\ddagger}$ 19.1
$\Delta S^{\ddagger}$ -1.7



k_r 1.0



k_r 20.4
$\Delta H^{\ddagger}$ 16.8
$\Delta S^{\ddagger}$ -11.4

CHART I.

constants and associated activation parameters for the alkaline hydrolysis of a number of cyclopentane and norbornane acetates (Chart I).

Inspection of the data presented in Chart I as well as the temperature dependence of $\Delta S^{\ddagger}$ reveals the following:

(1) Alkaline hydrolysis is facilitated by a neighboring hydroxyl group in both the vic-cyclopentanediol monoacetates and in exo-2-acetoxy-syn-7-hydroxynorbornane. The facilitation is not due to an inductive effect (compare trans-hydroxy to trans-methoxycyclopentyl acetate).

(2) The facilitation is characterized by a large positive change of both $\Delta H^{\ddagger}$ and $\Delta S^{\ddagger}$. The compensation by $\Delta H^{\ddagger}$ is not sufficient (78°) to prevent $\Delta F^{\ddagger}$ becoming more negative due to the overwhelming importance of $-T\Delta S^{\ddagger}$.

(3) The extent of facilitation is markedly temperature dependent and is only of the order 2 to 3x at 25°.

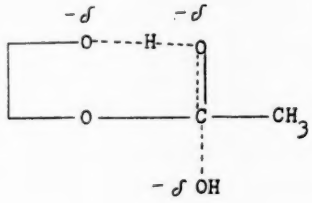
(4) The mechanism proposed by Henbest and Lovell is incorrect since marked enhancements of alkaline hydrolysis of esters must be ascribed to an increase in the rate constant associated with the attack of the $^{\ominus}OH$ on the ester carbonyl.[8] Also, and of greater significance, is the finding that the trans as well as the cis cyclopentanediol monoacetates exhibit facilitation. The Henbest mechanism could not apply to the trans ester.

(5) For the alkaline hydrolysis of ethyl acetate the $\Delta\Delta H^{\ddagger}$ and $\Delta\Delta S^{\ddagger}$ values associated with transfer from water to ethanol-water mixture resembles the $\Delta\Delta H^{\ddagger}$ and $\Delta\Delta S^{\ddagger}$ values noted on substitution of a neighboring hydroxyl group. Thus, ethyl acetate hydrolysis is slower in ethanol-water at 25° than in water but at 78° it should be faster in ethanol-water than in water.[9]

[8] T.C. Bruice and U.K. Pandit, J.Amer.Chem.Soc. 82, 5858 (1960).

[9] Extrapolated from the data of J.E. Potts and E.S. Amis, J.Amer.Chem.Soc. 71, 2112 (1949).

We suggest that the facilitation associated with the presence of a neighboring hydroxyl group is due to a microscopic medium effect and/or stabilization of the transition state associated with the attack of the hydroxide ion.



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Tetrahedron Letters No.8, pp. 267-269, 1961. Pergamon Press Ltd. Printed in Great Britain.

PRO-ANTHOCYANIDINE AUS DEN FRÜCHTEN DES WEIßDORNS (CRATAEGUS OXYACANTHA)

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(Received 10 April 1961)

DER alkoholische Extrakt frischer Früchte von Crataegus oxyacantha enthält neben dem schon früher darin gefundenen Quercetin- 3 - galactosid[1] und dem (-)-Epicatechin[2] 2 weitere Substanzen aus der mannigfaltigen und umfangreichen Gruppe der Pro-anthocyanidine,[3] die alle Stoffe umfaßt, die bei der Einwirkung von Mineralsäure Anthocyanidine ergeben. Der eine dieser Stoffe liefert bei der vorsichtigen Hydrolyse mit Säure (-)-Epicatechin und Cyanidin. Über ihn wird hier berichtet. Der andere ist in geringerer Menge vertreten und bildet Cyanidin und ein anderes Anthocyanidin.

Das Pro-cyanidin hat die Zusammensetzung $C_{30}H_{26}O_{13}$ [$C_{30}H_{26}O_{13}\cdot 1H_2O$ (612) Ber. C 58.82, H 4.57, H_2O 2.9; Gef. 59.28, H 4.75, H_2O 3.1, $[\alpha]_{578}^{25} = +23^\circ$ (c=2, Aceton/Wasser 1:1)]. Es enthält 8 phenolische und 2 aliphatische Hydroxyle sowie 3 Äthersauerstoffatome. Mit Wasserstoff-ion bildet es Epicatechin und Cyanidin-ion. Mit Diazomethan entsteht der Octamethyläther ($C_{38}H_{42}O_{13}\cdot 1H_2O$ Ber. C 62.98, H 6.07, OCH_3 34.19, Molgew. 724; Gef. C 62.70, H 6.12, OCH_3 34.24, Molgew. 677; Diacetyloctamethyläther $C_{42}H_{46}O_{15}$ (790) Ber. OCH_3 31.43, $COCH_3$ 10.8; Gef. OCH_3 31.55, $COCH_3$ 10.5; Deka-acetat $C_{50}H_{46}O_{23}$ (1014) Ber. C 59.14, H 4.59, $COCH_3$ 42.4; Gef. C 59.44, H 5.03, $COCH_3$ 42.7).

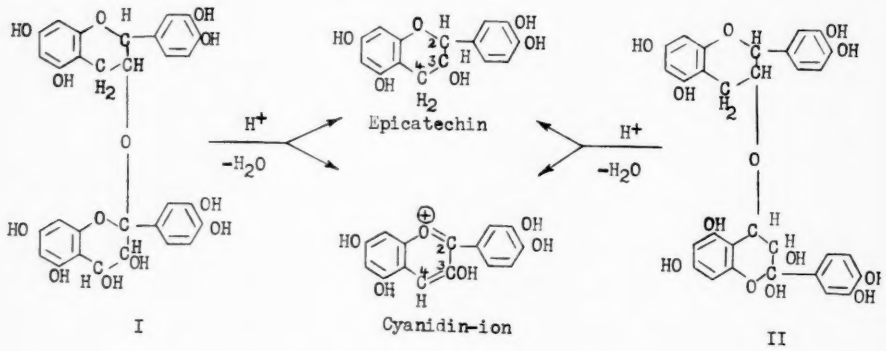
[1] U. Fiedler, Naturwiss. 40, 226 (1953).

[2] K. Weinges, unveröffentlicht; K.Freudenberg, Experientia 16, 101, Anm.1 (1960).

[3] K.Freudenberg und K. Weinges, Tetrahedron 8, 336 (1960).

Der Octamethyläther liefert bei der Hydrolyse Tetramethyl-epicatechin und Tetramethyl-cyanidin. Das Kohlenstoffatom 3 des Epicatechins ist also an der Ätherbindung zwischen den beiden Molekülhälften beteiligt. Für die Bindung der anderen Molekülhälfte kommen die Kohlenstoffatome 2 oder 4 in Betracht. Im ersten Falle ergibt sich die Formel I, im zweiten Falle II. Wir geben der Formel I den Vorzug, ohne die Formel II endgültig ausschließen zu können.

Obwohl das Pro-cyanidin und seine Derivate amorph sind, liefern Molekulargewichtsbestimmung und Analysen brauchbare Werte, die zu den Formeln I und II führen. Eine Substanz der Formel II sollte mit einiger Wahrscheinlichkeit Ketonreaktionen zeigen, was nicht der Fall ist. I ist ein Ketal, das die Stabilität der Verbindung gegenüber Alkali verstehen läßt,



während II ein Halbketal ist, das ähnlich wie Glucose durch Alkali zur Mutarotation angeregt werden sollte. Hierfür liegen keine Anzeichen vor. Nach beiden Formeln ist die Substanz ein Äther zwischen Epicatechin und einem Flavan-triol-2.3.4, das als hydratisiertes Pseudo-cyanidin anzusehen ist. Ein solches Triol ist ohne Zweifel sehr instabil und dürfte durch die Ätherbindung nach I gerade an seiner empfindlichen Stelle stabilisiert sein.

Im Gegensatz zu Th.Bersin[4] haben wir im Crataegus kein Glycosid eines Pro-cyanidins gefunden. Forsyth und Roberts[5] haben aus Kakaobohnen ein Pro-cyanidin isoliert, das gleichfalls mit H-ion in (-)-Epicatechin und Cyanidin zerfällt. Ob es mit unserem Pro-cyanidin übereinstimmt, können wir nicht entscheiden. Aus dem chemischen Verhalten schließen die britischen Autoren auf ein offenes Halbketal zwischen dem 3-Hydroxyl des Epicatechins und einem Flavanol-2-on-3. Gegen ihre Auffassung kann eingewandt werden[6], daß offene, d.h. nicht zum Ring geschlossene Halbacetale bisher in der Natur nicht angetroffen worden sind.

[4] Schweizerische Apothekerzeitung 95, 403 (1957).

[5] W.G.C. Forsyth und J.B. Roberts, Chem. & Ind. 755 (1958).

[6] K. Freudenberg, Diskussionsbemerkung auf dem Treffen von Plant Phenolic Group, London 6.Jan.1959; K.Freudenberg und K. Weinges in T.A. Geissman, Chemistry of Flavonoids Kap.7. Pergamon Press, London (1961).

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INDOLE ALKALOIDS

PRESENCE OF A N_a-CH_3 GROUP IN VOACHALOTINE

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THE presence of a N-CH_3 group in voachalotine (the major alkaloid of Voacanga Chalotiana), O-acetylvoachalotine, voachalotinol and O,O-diacetyl-voachalotinol was reported earlier.[1]

We have now been able to show conclusively that the methylated nitrogen atom is the indolic nitrogen (N_a). This finding is of particular interest because voachalotine thus appears to be the first true indole alkaloid* bearing a methyl group on N_a. The nearest approach to this structural feature is to be found in the mavacurine[3] and eburnamine[4] series, in which N_a is involved in an extra ring, formally built up by internal cyclization on N_a.

The presence of a N_a-CH_3 group in voachalotine is supported by the following evidence.

* By "true indole alkaloid" we mean an alkaloid in which the aromatic chromophore is limited to the indole chromophore, with or without substituents. According to this definition, alstonidine,[2] which has an indole N-methyl-harmane structure (N_a substituted-β-carboline chromophore), is not a "true indole alkaloid".

1 J. Pecher, N. Defay, M. Gauthier, J. Peeters, R.H. Martin and A. Vandermeers, Chem. & Ind. 1481 (1960).

2 H. Boaz, R.C. Elderfield and E. Schenker, J.Amer.Pharm.Assoc. 46, 510 (1957).

3 H. Bickel, H. Schmid and P. Karrer, Helv.Chim.Acta 38, 649 (1955).

4 M.F. Bartlett and W.I. Taylor, J.Amer.Chem.Soc. 82, 5941 (1960).

Nuclear magnetic resonance spectroscopy (cf. Table 1)

The 56.4 mc/sec NMR spectra of voachalotine, O-acetylvoachalotine, O,O-diacetylvoachalotinol and anhydrovoachalotine,* all show a sharp 3 proton singlet at $\tau = 6.42$, which certainly arises from a N_a-CH_3 group. This assignment is confirmed :

(a) by the presence of a similar peak in the specta of known N-methylindoles : N-methyl-1,2,3,4-tetrahydrocarbazole and N-methyl-3-[2-(methylamino)ethyl]indole;[5]

(b) by the absence of this band in indole derivatives characterized by an unsubstituted N_a-H group : 1,2,3,4-tetrahydrocarbazole, ibogaine and voacangine.

As was expected, the 3 proton singlet ($\tau = 6.42$) of voachalotine is shifted to $\tau = 7.64$ in perhydrovoachalotine.** This new peak is indeed characteristic of an aliphatic N-CH_3 group. This follows from comparison with suitable models, such as gelsemine,[6] 3-[2-(dimethylamino) ethyl]indole[5] and N-methyl-3-[2-(methylamino)ethyl]indole.[5]

These facts alone, show quite clearly the presence of a N_a-CH_3 group in voachalotine.

Infra-red spectroscopy (cf. Table 1)

The question of the presence or the absence of a N-H group in voachalotine could not be settled by a simple inspection of its infra-red spectrum. On the other hand, it is quite clear that there is no such structural feature in O-acetylvoachalotine, O-O-diacetylvoachalotinol and anhydrovoachalotine (absence of a characteristic band in the 2.9-3μ region - LiF prism-CS_2). In this connexion, it should be noted that the I.R. spectra

* Anhydrovoachalotine (m.p. 226-229°) was obtained in an attempted Oppenauer oxidation of voachalotine.

** Perhydrovoachalotine was prepared by catalytic hydrogenation of voachalotine, using Adam's platinum in MeOH/HCl.

[5] L.A. Cohen, J.W. Daly, H. Kny and B. Witkop, J.Amer.Chem.Soc. 82, 2184(1960).

[6] H. Conroy and J.K. Chakrabarti, Tetrahedron Letters No.4, 6 (1959).

TABLE 1

	NMR (τ)			I.R. (μ)	U.V. (mμ) methanol		
	N_α-H	N_α-CH_3	N_β-CH_3		λ_{max}	λ_{min}	λ_{max}
Voachalotine		6.42		2.78w	229	252	285
O-Acetylvoachalotine		6.42			229	251	285
Voachalotinol				2.88-2.98	229	251	285
O,O-Diacetylvoachalotinol		6.42			229	251	285
Anhydrovoachalotine		6.42			229	251	284
Perhydrovoachalotine		7.64					
N-Methyl-1,2,3,4-tetrahydrocarbazole		6.42			231	253	286
1,2,3,4-Tetrahydrocarbazole	2.54			2.96	228	251	282.5
Ibogaine	2.46			2.97			
Voacangine	2.25			2.92			
Gelsemine[6]			7.84				
3-[2-Dimethylamino)ethyl]indole[5]			7.65				
N-Methyl-3-[2-(methylamino)ethyl]indole[5]		6.35	7.62				
N-Methyl-indole[5]		6.63					

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of voacangine and of ibogaine both have a strong band in this region (2.92μ and 2.97μ, respectively).

Ultra-violet spectroscopy (cf. Table 1)

The long wavelength maximum of voachalotine, O-acetylvoachalotine, voachalotinol, O,O-diacetylvoachalotinol and anhydrovoachalotine is situated within experimental errors of the long wavelength maximum of N-methyl-1,2,3,4-tetrahydrocarbazole, and shows a slight bathochromic shift as compared to that of 1,2,3,4-tetrahydrocarbazole. These findings, if not conclusive by themselves, confirm the NMR and I.R. evidence.

The presence of a N_a-CH_3 group in voachalotine and its absence in voacangine easily explains the following facts, if it is assumed that in both molecules the methoxycarbonyl group is in the same relative position to N_a.

(1) The wavelength of the C=O vibration (methoxycarbonyl group) in voachalotine is quite normal (5.75μ). On the other hand, the corresponding band in voacangine is shifted to longer wavelength (5.84μ). This shift is probably due to the formation of a hydrogen bond between N_a-H and the methoxycarbonyl group in voacangine. Such a bond is of course excluded in voachalotine.

(2) The alcohol prepared by reduction of the methoxycarbonyl group of voacristine (voacangarine) reacts with acetone to give a cyclic ketal.[7] We have recentlyfound that, under the same experimental conditions, voachalotinol remains unchanged. Here again, the presence of a N_a-CH_3 group in voachalotine would prevent the formation of the cyclic derivative.

The authors wish to thank Dr. J Nasielski for many helpful discussions on NMR spectra and (Miss) F. Evrard for recording some of the I.R. spectra. One of them (M.K.) is indebted to the "Institut pour la Recherche Scientifique dans l'Industrie et l'Agriculture" (IRSIA), for the award of a fellowship.

[7] D. Stauffacher and E. Seebeck, Helv.Chim.Acta 41, 169 (1958).

Tetrahedron Letters No.8 pp.274-279, 1961. Pergamon Press Ltd. Printed in Great Britain.

MAGNETIC SHIELDINGS AND THE ELECTRONIC STRUCTURES OF AROMATIC MOLECULES

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(Received 20 April 1961)

A NUMBER of discussions of the F^{19} and H^{1} nuclear magnetic resonance spectra of aromatic compounds have appeared, and it has been demonstrated that the shieldings are closely related to the separated σ-constants of Taft.[1-3] Further correlations with π-electron distributions have been proposed recently for both fluorine[4] and hydrogen[5] shieldings. Our studies of natural abundance C^{13} nuclear magnetic resonance spectra of aromatic hydrocarbons,[6] of phenols and related compounds,[6] of other substituted

* Multiple Fellowship on Silicones sustained by the Dow Corning Corporation and Corning Glass Works.

1 R.W. Taft, Jr., S. Ehrenson, I.C. Lewis and R.E. Glick, J.Amer.Chem.Soc. 81, 5352 (1959).

2 R.W. Taft, Jr., J.Phys.Chem. 64, 1805 (1960). This review, and Ref. 1, may be consulted for references to earlier work on the F^{19} shieldings.

3 R.R. Fraser, Canad.J.Chem. 38, 2226 (1960); which may be consulted for earlier references on H^{1} shieldings.

4 K. Ito, K. Inukai and T. Isobe, Bull.Chem.Soc.Japan 33, 315 (1960).

5 G. Fraenkel, R.E. Carter, A.McLachlan and J.H. Richards, J.Amer.Chem.Soc. 82, 5846 (1960).

6 P.C. Lauterbur, J.Amer.Chem.Soc. In press.

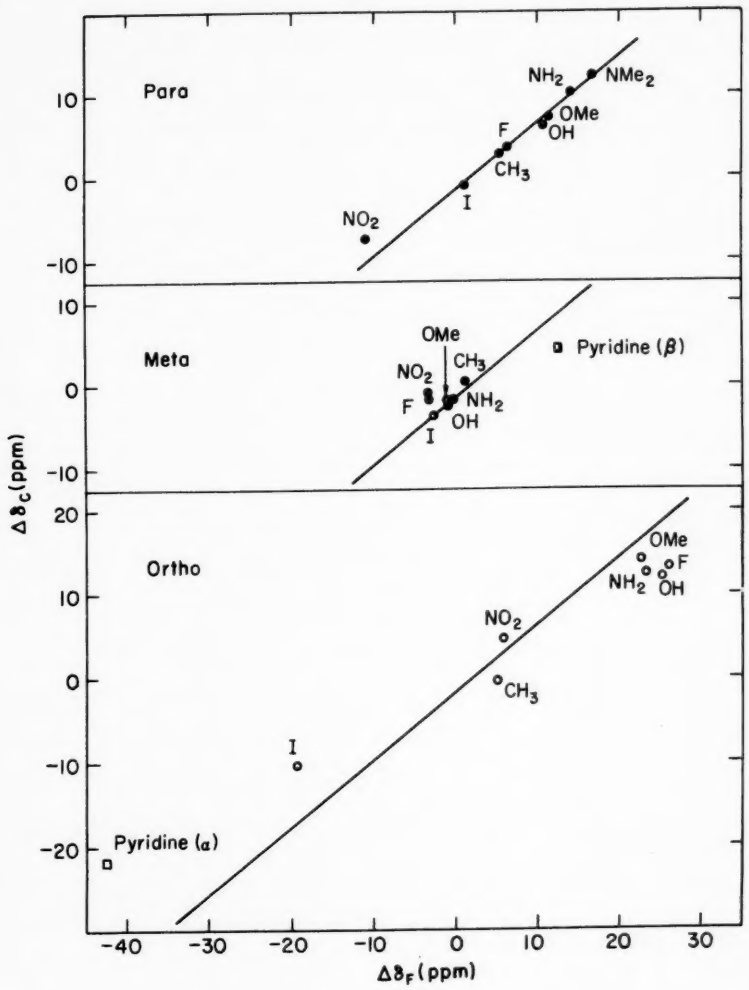

FIG. 1

C^{13} Shieldings (relative to benzene) in substituted benzenes and in pyridine vs. F^{19} shieldings (relative to fluorobenzene) in the corresponding substituted fluorobenzenes and in fluoropyridines.

benzenes[7] and of aromatic heterocyclics[7] show that carbon shieldings in the parent compounds are also closely related to the above parameters and may often be more simply related to the ground state electron distributions than are the fluorine shieldings in their fluorine derivatives. The interpreation of fluorine shieldings is complicated by the possibility of resonance interactions of the fluorine with other substituents[1,2,8] and of other deviations from additivity, especially in the ortho-fluorinated compounds. Hydrogen shieldings are subject to long-range magnetic effects[9] and to large solvent shifts[10,11] and may be expected to be closely correlated with the electronic distribution in the ring only within closely related series of compounds.

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The comparison of fluorine[4,12] and carbon[6,7] shieldings in Fig. 1 illustrates the above points. The para substituents, except for the one +R substituent, NO_2, give points falling on a straight line of slope 0.8. The fluorine nucleus in p-nitrofluorobenzene is about 3 p.p.m. less shielded than would have been expected by comparison with the para carbon in nitrobenzene, quantitatively confirming Taft's suggestion[2] that the resonance interaction of the nitro group with the fluorine is responsible for the deviation of the p-nitrofluorobenzene point from his plot of fluorine shieldings against the σ_R^o-parameter. The shieldings of fluorine ortho to

[7] P.C. Lauterbur, to be published.

[8] R.W. Taft, Jr., R.E. Glick, I.C. Lewis, I.Fox and S. Ehrenson, J.Amer.Chem.Soc. 82, 756 (1960).

[9] For a review, see L.M. Jackman, Applications of Nuclear Magnetic Resonance Spectroscopy in Organic Chemistry Chap.7. Pergamon Press, London, New York (1959)

[10] T. Schaefer and W.G. Schneider, J.Chem.Phys. 32, 1218, 1224 (1960), and references cited therein.

[11] A.D. Buckingham, T. Schaefer and W.G. Schneider, J.Chem.Phys. 32, 1227 (1960).

[12] H.S. Gutowsky, D.W. McCall, B.R. McGarvey and L.H. Meyer, J.Amer.Chem.Soc. 74, 4809 (1952).

OH, OMe, NH_2, F and CH_3 are all greater than would be expected on the basis of the *para* relationship; the smaller shielding of the *ortho* nitro compound may be the result of the conjugative interaction used to explain the decrease in shielding in the *para* compound.

The best set of measurements of hydrogen shieldings in a variety of substituted benzenes is that of Fraser[3]. A plot of his hydrogen shieldings against the carbon shieldings in the same compounds is shown in Fig. 2. The *meta* hydrogen shieldings have been adjusted by Fraser to compensate for the effects of the two methyl groups.

The *para* points fall close to a straight line with a slope of about 16. Combining this with an estimate[5] of a coefficient of 10 p.p.m. per π-electron for hydrogen shifts, the coefficient for carbon is found to be about 160 p.p.m. per electron, in good agreement with an earlier estimate.[6] It thus appears likely that the π-electron charges play an important role in determining magnetic shieldings in aromatic molecules.

The possibility of determining such charges suggests a number of investigations. One of the most promising is the study of interactions between two or more substituents on the same ring. It has been found that the effects of substituents and of hetero atoms on ring carbon shieldings are usually nearly additive, but that definite small deviations from additivity are found for all relative positions and types of substituents. The deviations are especially pronounced when *ortho* groups are present, as one would expect. The *ortho* effects are of two types; those in which only the atoms bearing the *ortho* groups are affected, and those in which the long-range interactions are changed because of steric inhibition of resonance. The interactions between methyl groups and CH_3, OH, NH_2, F and I are of the former type; in the most extreme example the shielding of the carbon bearing the iodine is decreased by almost 14 p.p.m. by two *ortho* methyl groups, but there is no anomalous effect at the *para* position.[7]

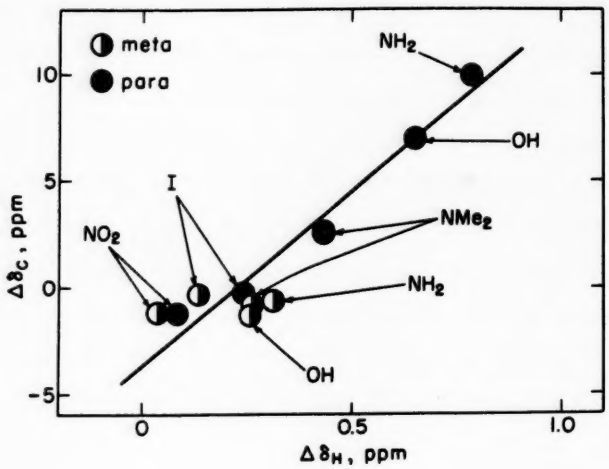

FIG. 2.

C^{13} Shieldings vs. H^1 shieldings in 2,6-dimethyl-1-substituted benzenes (relative to benzene).

The shieldings of para carbons are, however, markedly affected by methyl substitution ortho to groups whose resonance interactions with the ring may be reduced by steric effects. The relative para carbon shieldings in N,N-dimethylaniline, N,N-dimethyl-o-toluidine and N,N,2,6-tetramethylaniline are decreased by ortho methyl substitution,[7] in quantitative agreement with the calculated variation of the electron density[13] with the angle of twist of the dimethylamino group.[14] The para shieldings in nitrobenzene increase with ortho methyl substitution, paralleling the changes in the electronic spectra, dipole moments and molar refractions[15] in very satisfactory fashion. An anomaly in the nitrobenzene shieldings may be noted. Fig. 1 shows that

[13] E.G. McRae and L. Goodman, J.Chem.Phys. 29, 334 (1958).

[14] E.G. McRae and L. Goodman, Mol.Spectr. 2, 464 (1958).

[15] B.M. Wepster, Rec.Trav.Chim. 76, 335 (1957).

both fluorine and carbon are more shielded at the ortho position than are the reference compounds, implying that there is a π-electron density greater than unity on the ortho carbons. No theoretical calculations support this possibility and it may be that major distortions of the σ-bond framework[16] can affect the shieldings.

A number of unexpected deviations from additivity of the carbon shieldings in polysubstituted benzenes have been observed and will be reported in detail elsewhere. It seems certain that the ability to detect the magnetic shielding effects of substituents and their interactions at each carbon atom will lead to a more detailed understanding of aromatic molecules.

J. Trotter, Tetrahedron 8, 13 (1960).

Tetrahedron Letters No.8, pp. 280-284, 1961. Pergamon Press Ltd. Printed in Great Britain.

ABSOLUTE CONFIGURATION OF THE SUBSTITUENT AT C-7 IN GUAIOL

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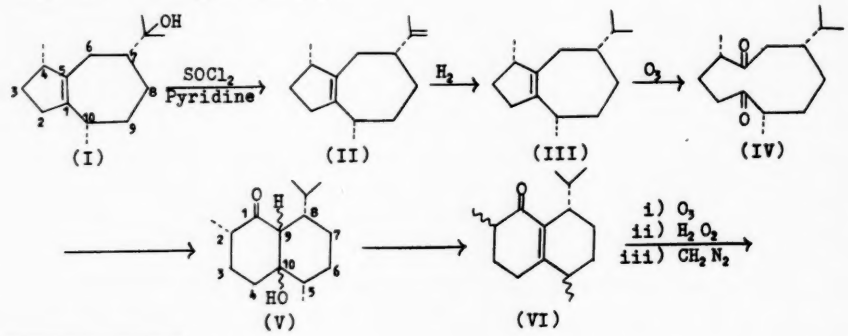
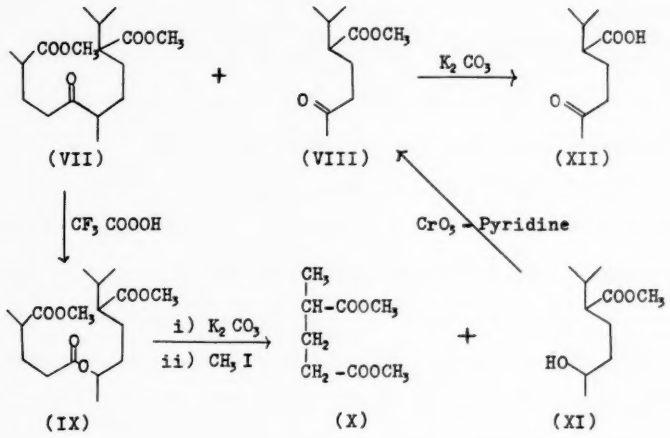
IN the preceding papers,[1] it was established that both the C-4 and the C-10 methyl groups in guaiol (I) possess the α-configuration. Now the question remains as to whether the substituent at C-7 in guaiol is α- or β-oriented.

In this experiment, an attempt was made to determine the absolute configuration of the hydroxyisopropyl group at C-7 in guaiol by degradation of 10-hydroxy-2,5-dimethyl-8-isopropyl-decalone-1 (V) which was reported in the previous paper.[2]



[1] K. Takeda and H. Minato, Tetrahedron Letters No. 22, 33 (1960); K. Takeda and H. Minato, Chem. Pharm. Bull. (Japan) 9 (1961), in press; H. Minato, Ibid. 9 (1961), in press.

[2] K. Takeda, H. Minato and S. Nosaka, Tetrahedron (1961), in press.



The ten-membered ring diketone (IV) was produced through II and III and possesses a bulky isopropyl group. This fact suggests that the conformation possessing the thermodynamically more stable equatorial-like isopropyl group at C-7 is preferred in IV.

When IV was heated at 190-200° without a solvent, or treated with acetic acid under reflux for 1 hr, or with 0.1 N solution of sodium methoxide in methanol under reflux for 1 hr, the result in each case was that the same product, V, was obtained. It would therefore be expected that the isopropyl group in V also possesses the more stable equatorial configuration. This assumption was established by observation of the NMR spectrum of V in chloroform. The spectrum at 56.4 Mc/sec shows a doublet signal (4.97 p.p.m. referred to chloroform) of a proton attached to a carbon atom which is α to a carbonyl group. The fact that the signal is split into a doublet with a 10.5 c.p.s. spin coupling constant indicates the existence of one proton on the adjacent carbon atom. This interpretation of the NMR spectrum leads to the conclusion that the hydrogen atoms at C-8 and C-9 are oriented

trans-diaxially[3] to one another and that the isopropyl group at C-8 is equatorial in V.

In view of the course of production of V, the C-4 and C-10 methyl groups and the C-7 hydroxyisopropyl group in guaiol are considered to have maintained these original configurations in V.

Treatment of V with 1 mole sodium hydride in absolute toluene followed by mesylation with mesyl chloride and then chromatography on neutral alumina gave VI and two stereoisomers of V, m.p. 112-112.5°, $[\alpha]_D$ +24.5° and m.p. 130-131.5°, $[\alpha]_D$ -31.4°, as by-products. During the course of this reaction, it is obvious that epimerisation of the quasi-equatorial isopropyl group at C-8 in VI does not occur, although its racemisation may occur to some extent.

Ozonolysis of this α,β-unsaturated ketone (VI) in ethyl acetate followed by hydrogen peroxide oxidation in a neutral medium afforded a mixture of carboxylic acids. The methyl ester obtained by the action of diazomethane was chromatographed on neutral alumina and fractionated to obtain the following fractions: Fraction no. 1, a colorless mobile oil, b.p. 70-84°/1 mm and Fraction no. 2, a pale yellow oil, b.p. 144-145°/1 mm. Fraction no. 2 was the dimethyl ester of the expected keto-dibasic acid (VII), $[\alpha]_D$ -9.8° (Found: C, 64.90; H, 9.47. $C_{17}H_{30}O_5$ requires: C, 64.94; H, 9.62. I.R. ν_{film} 1738, 1713 cm^{-1}), which in turn was rearranged by the Baeyer-Villiger reaction with trifluoroperacetic acid to the ester (IX), b.p. 142-143°/1 mm, $[\alpha]_D$ -2.4° (Found: C, 62.25;

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[3] A. D. Cohen, N. Sheppard and J. J. Turner, Proc. Chem. Soc. 118 (1958); R. U. Lemieux, R. K. Kullnig, H. J. Bernstein and W. G. Schneider, J. Amer. Chem. Soc. 79, 1005 (1957), 80, 6098 (1958); R. U. Lemieux, R. K. Kullnig and R. Y. Moir, Ibid. 80, 2237 (1958).

H, 9.31. $C_{17}H_{30}O_6$ requires: C, 61.79; H, 9.15. I.R. $_{film}$ 1740 cm^{-1}). Treatment of Fraction no. 1 with Girard's reagent T gave levorotatory methyl α-isopropyl-γ-acetobutyrate (VIII), b.p. 81-82°/3 mm, $[\alpha]_D$ -9.0° (Found: C, 64.19; H, 9.87. $C_{10}H_{18}O_3$ requires: C, 64.49; H, 9.74. I.R. $_{film}$ 1733, 1712 cm^{-1}). This ketoester gave a semicarbazone, colorless needles, m.p. 128-129.5°, $[\alpha]_D$ -1.2° (Found: C, 54.59; H, 8.82; N, 16.98. $C_{11}H_{21}O_3N_3$ requires: C, 54.30; H, 8.70; N, 17.27).

On the other hand, IX was saponified by potassium carbonate in methanol, and its potassium salt was refluxed with methyl iodide in absolute methanol to give a mixture of methyl esters. Chromatography of this mixture on neutral alumina afforded methyl α-methylglutarate (X) as well as methyl α-isopropyl-δ-hydroxy-caproate (XI), b.p. 110-111°/5 mm, $[\alpha]_D$ +1.3° (Found: C, 63.60; H, 10.83. $C_{10}H_{20}O_3$ requires: C, 63.79; H, 10.71. I.R. $_{film}$ 3421, 1733 cm^{-1}), which was oxidized to VIII with chromium trioxide-pyridine. Saponification of VIII with potassium carbonate in methanol gave levorotatory α-isopropyl-γ-acetobutyric acid (XII), b.p. 147-150°/2 mm (bath temp), $[\alpha]_D$ -5.0° (semicarbazone, colorless needles, m.p. 140-142°. Found: C, 52.38; H, 8.51; N, 18.08. $C_{10}H_{19}O_3N_3$ requires: C, 52.38; H, 8.35; N, 18.33). Wallach[4,5] obtained levorotatory α-isopropylglutaric acid, m.p. 92-93°, $[\alpha]_D$ -15.82°, by oxidation of levorotatory α-isopropyl-γ-acetobutyric acid, b.p. 175-180°/19 mm, $[\alpha]_D$ -6.18°, which was derived from dextrorotatory fenchone, with sodium hypobromite.

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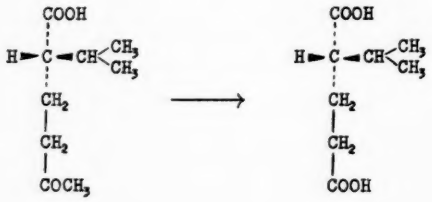
[4] O. Wallach, Ann. 369, 63 (1909), 379, 182 (1911).

[5] K. Frendenberg and W. Lwowski, Ann. 587, 213 (1954).

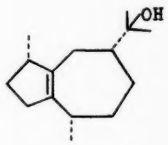
	Acid		Ester	
	$[\alpha]_D$	Semi-carbazone m.p.	$[\alpha]_D$	$[\alpha]_D$ of semi-carbazone
VIII	-5.0° (in dioxane)	140-142°	-9.0° (in dioxane)	-1.2° (in dioxane)
Wallach's VIII	-6.18° (without solvent)	138-140°	-5.58°*	----

* Ethyl ester (J. L. Simonsen, J. Chem. Soc. 119, 1646, 1653 (1921)).

Since Fredga[6] established that levorotatory α-isopropylglutaric acid has the S** (or D)-configuration, VIII should belong to the S-series.



(VIII) S-(-)-isopropylglutaric acid



(XIII)

Further, as the C-8 isopropyl group in 10-hydroxy-2,5-dimethyl-8-isopropyl-decalone-1 (V) possesses the α-configuration, guaiol should be represented by XIII.

Acknowledgement —— The author expresses his gratitude to Mr. M. Tori for his aid in the determination and interpretation of the NMR spectra.

6 A. Fredga, Acta. chem. Scand. 1, 371 (1947).

** The configurational symbol S is based on the nomenclature sequence rule (R. S. Cahn, C. K. Ingold and V. Prelog, Experientia 12, 81 (1956)).

Tetrahedron Letters No. 9, pp. 285-288, 1961. Pergamon Press Ltd. Printed in Great Britain.

A REVISED STRUCTURE FOR PTEROCARPIN

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(Received 11 May 1961)

THE recent isolation of the antifungal glucoside trifolirhizin and its aglycone from Trifolium pratense L.[1,2] and the methylation of the aglycone to pterocarpin has drawn our attention to the structure of the latter compound.

The subfamily Papilionatae is known as a rich source of isoflavanoid substances. A literature scrutiny of 2'-oxygenated isoflavanoids that have a dimethoxy or a methylenedioxy group in the B-ring revealed an interesting observation. All the investigated substances (rotenoid type compounds,[3,4] pachyrrhizin,[5] jamaicin,[6] erosnin,[7] sophorol[8]) except pterocarpin have the

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* Varian Associates, Palo Alto, California.

1 P. K. Hietala, Ann.Acad.Sci.Fennicae, Series A II Chemica 100, 61 (1960).

2 J. B. Bredenberg and P. K. Hietala, Acta Chem.Scand. 15, In press (1961).

3 W. Karrer, Konstitution und Vorkommen der organischen Pflanzenstoffe references cited on pp. 572-579. Birkhäuser Verlag, Basel (1958).

4 N. Finch and W. D. Ollis, Proc.Chem.Soc. 176 (1960).

5 E. Simonitsch, M. Frei and H. Schmid, Monatsh. 88, 541 (1957).

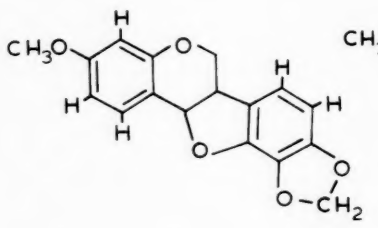
6 O. A. Stamm, H. Schmid and J. Büchi, Helv.Chim.Acta 41, 2006 (1958).

7 J. Eisenbeiss and H. Schmid, Helv.Chim.Acta 42, 61 (1959).

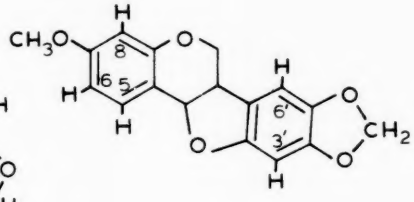
8 H. Suginome, Tetrahedron Letters No. 19, 16 (1960).

oxygens in the 4',5'-positions. In the structure proposed for pterocarpin (I)[9,10] the oxygens are in the 3',4'-positions. This deviation from the biogenetically related compounds, particularly sophorol, made a reinvestigation of the structure necessary, especially as the evidence for the B-ring oxidation pattern[10] does not seem to be conclusive, since it rests on the comparison of the infrared spectra of a reaction product of pterocarpin with a synthetic compound.

An NMR spectrum of pterocarpin (Fig. 1) was taken in deuterated chloroform at 60 mc/sec, using a Varian Associates A-60 Spectrometer. It provides unequivocal proof of the superiority of structure II over structure I



I



II

Aromatic protons which are not adjacent to an oxygen will be found near the ordinary position for unsubstituted benzene, i.e. between δ = 7.3 and 7.4 p.p.m. (relative to tetramethylsilane).[11] If an aromatic proton is adjacent to one oxygen it will be shifted upfield to the region between δ = 6.7 and 6.8 p.p.m., while if it is adjacent to two oxygens

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9 A. McGookin, A. Robertson and W. B. Whalley, J.Chem.Soc. 787 (1940).

10 A. Robertson and W. B. Whalley, J.Chem.Soc. 1440 (1954).

11 Chemical shifts, δ, were measured in parts per million relative to the reference tetramethylsilane taken as zero and were read directly from the pre-calibrated chart paper. Increasing shifts correspond to a larger degree of unshielding of the protons being observed.

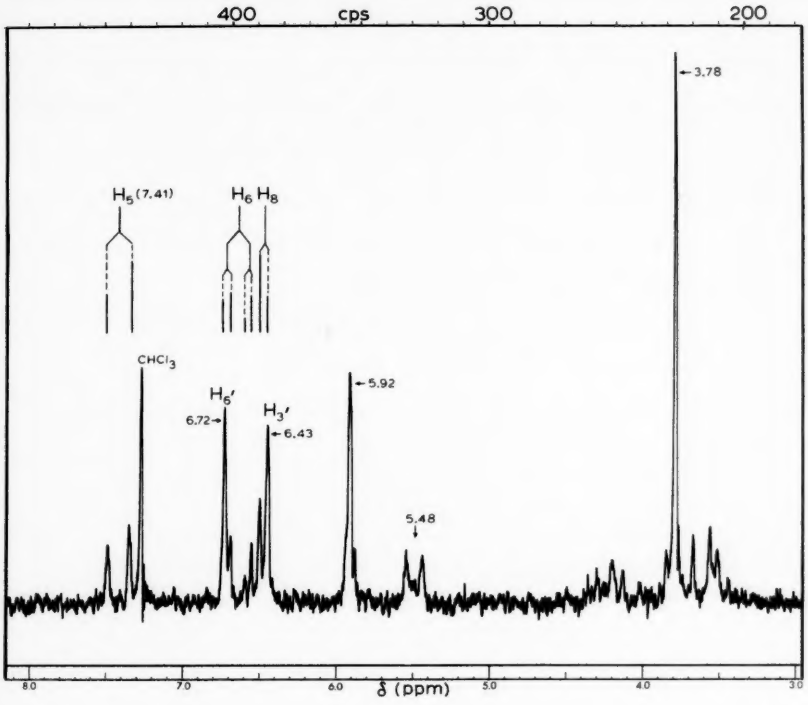

FIG. 1.

Nuclear magnetic resonance spectrum of pterocarpin.

it will be shifted to still higher magnetic field values (δ = 6.4 to 6.6).

A doublet centered at δ = 7.41 is found in the spectrum with a spin coupling of 9 cps, which shows that it must arise from a proton ortho to another aromatic proton. This can only be assigned as H_5. The remainder of the ABX pattern involving protons H_6 and H_8 is identified in Fig. 1 and accounts for the three protons of ring A. The remaining two strong peaks (at δ = 6.43 and 6.72) do not exhibit the spin-spin coupling which would be required for two aromatic protons ortho to one another. Furthermore, the chemical shifts correspond to one of these protons being adjacent to one oxygen and the other adjacent to two oxygens. The two strong peaks are

therefore assigned to H_3, and H_6, which proves that the structure of pterocarpin is II.

Other assignments in the spectrum are as follows. The methylene dioxy peak falls at $\delta = 5.92$. The CH group attached to ring A is found as a doublet centered at $\delta = 5.48$. The remaining protons in the molecule yield a complex multiplet surrounding the methoxyl resonance.

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Tetrahedron Letters No. 9, pp. 289-294, 1961. Pergamon Press Ltd. Printed in Great Britain.

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SYNTHESE UND EIGENSCHAFTEN DES THIALENS

(CYCLOPENTA-THIAPYRAN)

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(Received 9 May 1961)

DIE Synthese des Cyclopenta-thiapyrans, von uns Thialen (I) genannt und bereits 1957 als pseudo-Azulen vorausgesagt,[1] bereitete Schwierigkeiten. Es ist nur kurze Zeit als blau-violettes Öl beständig und wandelt sich vor allem bei Luftzutritt rasch in eine in den gebräuchlichen organischen Lösungsmitteln unlösliche und äusserst thermostabile Masse um, aus der es nicht mehr zu regenerieren ist. Nur in seinen relativ beständigen Lösungen kann I untersucht und weiterverarbeitet werden.

Im Gegensatz dazu ist das 1959 von Anderson und Mitarbeitern[2] synthetisierte orangerote kristalline pseudo-Azulen Isothialen (II) haltbar.

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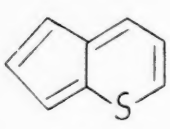
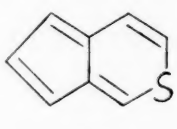
[1] R. Mayer, Angew.Chem. 69, 481 (1957).

[2] A.G. Anderson, Jr., W. F. Harrison, R. G. Anderson und A. G. Osborne, J.Amer.Chem.Soc. 81, 1255 (1959).

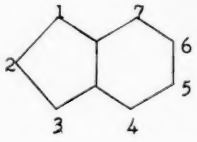
Diese Unterschiede werden auch aus Stabilitätsberechnungen deutlich, wonach II energetisch gegenüber I etwas begünstigt ist.[3]



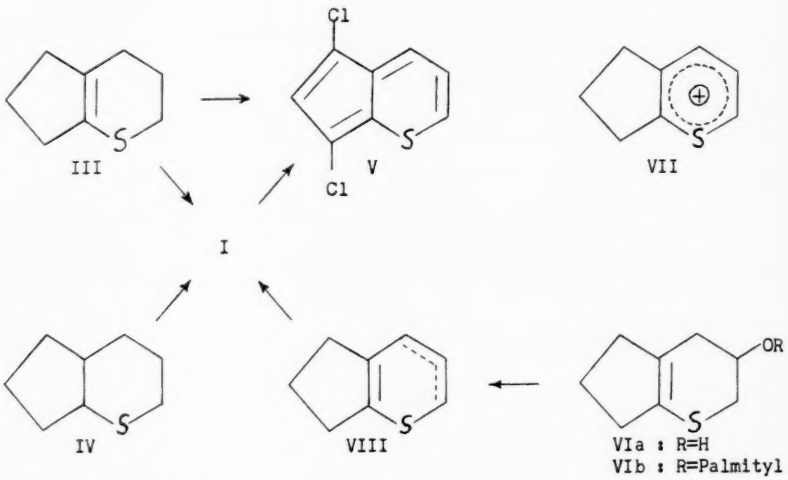
I



II



Ausgehend vom Cyclopentanon-o-carbonsäureester gelang die Synthese des Thialens (I) durch katalytische Dehydrierung des leicht erhältlichen III[4] oder IV[5] mit Pd-Kohle in der Dampfphase.



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[3] unveröffentlicht, R. Zahradník.

[4] I. Liebster, Diplomarbeit Universität Leipzig (1958); A. Hypko, Diplomarbeit Technische Hochschule Dresden (1960); vgl. R. Mayer und I. Liebster, Angew.Chem. 70, 105 (1958).

[5] Synthese wird anderenorts veröffentlicht.

I ist löslich in 30-proz. Schwefelsäure sowie in 85-proz. Phosphorsäure und lässt sich nach Verdünnen mit Wasser nur unter Verlusten in organische Lösungsmittel überführen. Auch die Reinigung an Al_2O_3 geringer Aktivität ist mit Substanzverlust verbunden.

Spektrum von I in Äther oder Cyclohexan: 232, (266), 348, 528-532 mμ
I wurde als Trinitrobenzolat (Schmp. 128-130°) charakterisiert (Gef. für $C_{14}H_9O_6N_3S$: C, 48,38; H, 2,76; N, 11,53; S, 9,72). Die Überführung des Hydrothialens III in I gelingt nur durch katalytische Dampfphasendehydrierung. Elementarer Schwefel verwandelt III bei höheren Temperaturen in eine rotorange, sublimierbare, bei 53° schmelzende Verbindung $C_8H_{10}S_2$, mit der wir uns ihrer neuartigen Struktur und ihres intensiven Pilzgeruches wegen gegenwärtig eingehend beschäftigen (vgl. l.c.[4]).

Bei der Dehydrierung von III mit Chloranil in siedendem Dekalin entsteht nicht I, sondern das Dichlorthialen V, das nach der Chromatographie an Al_2O_3 (blaue Zone) und Kristallisation aus wässrigem Alkohol in fast schwarzen Nadeln vom Schmp. 95,5-96,5° anfällt (Lösungsfarbe: blau) (Gef. für $C_8H_4SCl_2$: C, 47,94; H, 2,51; S, 15,97; Cl, 34,82). Hauptmaxima im Spektrum: 244, 278, 348, 568 mμ.

Das Thialen I entsteht auch aus dem Alkohol VIa beim Erwärmen der benzolischen Lösung in Gegenwart von p-Toluol-sulfosäure durch spontane Disproportionierung und Aromatisierung. Da I in saurer Lösung, vor allem in der Hitze, nicht besonders beständig ist, eignet sich diese Methode nicht zur präparativen Darstellung. Dazu muss vielmehr VIa oder VIb in der Dampfphase bei 260-300° über Al_2O_3 geleitet werden.

Die im Falle von VIb erhaltenen Produkte wurden massenspektroskopisch untersucht: Es dominiert erwartungsgemäss ein Peak der Masse 134. Ferner ist ein Peak der Masse 137 vorherrschend, der dem stabilen Ion VII entsprechen dürfte. Die Bildung des zu Grunde liegenden und dem Tropylium-Ion

analogen Grundkörpers unter den Bedingungen der Massenspektroskopie wurde übrigens an einem anderen Modell nachgewiesen[6] und auch experimentell gesichert.[7]

Die spontane Bildung von I aus VI ist nur durch Disproportionierung des nicht zu isolierenden Diens VIII verständlich. Seine Hydrierprodukte III und IV wurden massenspektroskopisch (140 und 142) nachgewiesen und zudem chromatographisch isoliert.

Eine kombinierte Dehydratisierung und Dehydrierung von VI in der Dampfphase an einem Palladium-Kohle-Kontakt führte zu keiner Verbesserung der Ausbeute an I.

VIa wurde aus o-Chlor-cyclopentanon und Monomercapto-aceton hergestellt.[5,8]

Entsprechend seinem quasiaromatischen Charakter ist Thialen (I) ausserordentlich leicht elektrophil substituierbar. So liess sich V auch direkt aus dem Thialen (I) mit N-Chlor-acetamid in Benzol und anschliessender chromatographischer Reinigung gewinnen (Gef. für $C_8H_4SCl_2$: C, 47,28; H, 2,08; Cl, 34,98). Schmp., Mischschmp. und Spektren waren mit dem aus III durch Behandlung mit Chloranil erhaltenen Präparat identisch.

Mit Oxalylchlorid reagiert I in Tetrachlorkohlenstofflösung bei Zimmertemperatur zu einer sowohl in Lösung als auch im festen Zustand roten Verbindung, die nach Veresterung mit Diazomethan und dreimaligem Umkristallisieren aus Cyclohexan bei 103-109,5° schmolz (Gef. für $C_{11}H_8O_3S$: C, 60,49; H, 3,96). Nach den Spektren, der Analyse und dem chemischen Verhalten handelt es sich dabei um den Monooxalylmethylester des Thialens. Im I.R.-

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[6] V. Hanuš und V. Čermák, Coll.Czech.Chem.Comm. 24, 1602 (1959).

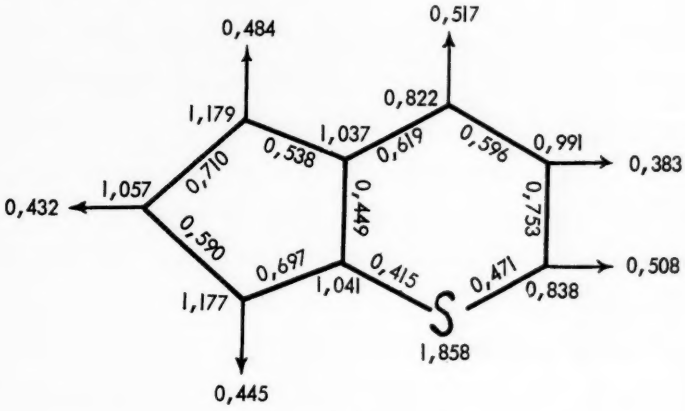
[7] R. Pettit, Tetrahedron Letters No. 23, 11 (1960).

[8] vgl. R. Kotva, Diplomarbeit Karls-Universität Prag (1957); O. Khek, Diplomarbeit Karls-Universität Prag (1958).

Spektrum liegt die der Ketogruppe zuzuordnende Bande bei 1620 cm^{-1}, die der Ester-CO-Gruppe entsprechende Bande bei 1732 cm^{-1}. Das möglicherweise vorliegende Isomerengemisch liess sich bisher noch nicht trennen.

Ein Gemisch von zwei isomeren Mononitro-thialenen wurde durch Umsetzung von I mit Tetranitromethan erhalten. Hier gelang es, das in der Chromatographiersäule schneller laufende Isomere in schönen orangen Nadeln zu isolieren (Schmp. 181,5-182°) (Gef. für $C_8H_5O_2NS$: N, 7,88).

Das Thialen I und das Isothialen II sind mit dem Azulen isoelektronisch. Die Berechnung[3] ergibt unter Verwendung der Orbitalenergien und Koeffizienten[9] für Azulen[10] in I und II für die Positionen 1 und 3 eine etwa gleiche maximale Elektronendichte:



Werte I.

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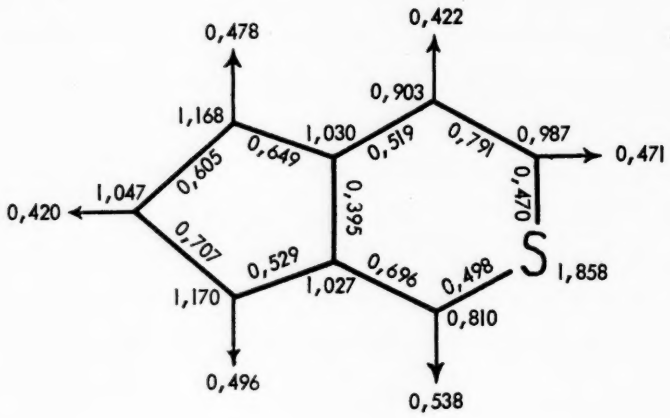
[9] H. C. Longuet-Higgins, Trans.Faraday Soc. 45, 173 (1949); C. A. Coulson, H. C. Longuet-Higgins, Proc.Roy.Soc. A 191, 39 (1947).

[10] C. A. Coulson and R. Daudel, Dictionary of Values of Molecular Constants, Vol. III (Erster Teil), S. 28. Centre National de la Recherche Scientifique.



Werte II.

Da beim Azulen und auch beim Isothialen (II)[11] in Übereinstimmung mit den Berechnungen elektrophile Substitutionen in 1 und 3 ablaufen und die Produkte strukturell gesichert sind, dürfen wir auch beim Thialen I eine elektrophile Substitution in 1 oder 3 erwarten. Nach den Berechnungen sind Positionen 7 (5) bei I bzw. 4 bei II nucleophilen bzw. radikalischen Substitutionen zugänglich.

Die Untersuchungen werden fortgeführt.

---

[11] A. G. Anderson, Jr. und W. F. Harrison, Tetrahedron Letters No. 2, 11 (1960).

Tetrahedron Letters No. 9, pp. 295-298, 1961. Pergamon Press Ltd. Printed in Great Britain.

A NOVEL ALKYLATION REACTION: THE REACTION OF HALOCYCLOPENTADIENES WITH PHOSPHOROUS ESTERS

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(Received 20 April 1961; in revised form 4 May 1961)

HEXACHLOROCYCLOPENTADIENE (I) reacts with alkyl phosphites to produce high yields of the corresponding alkyl phosphorochloridates and of 5-alkylpentachlorocyclopentadienes, RC_5Cl_5 (II), where R is the alkyl group of the phosphorous ester. Thus ethyl phosphite and I, when reacted in equimolar proportions, between 0 and 5°, yield ethyl phosphorochloridate, $(C_2H_5O)_2P(O)Cl$, (b.p. 39°/0.4 mm, n_D^{25} 1.4253; Lit.[1] b.p. 61°/2.5 mm) and 5-ethylpentachlorocyclopentadiene (III) (Found C, 31.5; H, 1.9; Cl, 66.7; $C_7H_5Cl_5$ requires C, 31.6; H, 1.9; Cl, 66.6%), in 93 and 96% yields, respectively. III (b.p. 50-51°/0.2 mm, n_D^{25} 1.5394) has spectra [λ_{max} (in isooctane) 308 mμ, log ε 3.26; infrared maxima 6.23, 8.11, 11.44, 12.41, 13.91 and 14.60μ] similar to those of I [λ_{max} (isooctane) 323 mμ, log ε 3.19; infrared maxima 6.24 (double bond stretching), 8.13, 8.78 and three bands in the C-Cl stretching region at 12.45, 14.21 and 14.75μ] and, in addition, III also has the modes of the ethyl group (C-H stretchings at 3.36, 3.42 and 3.50μ; C-H deformations at 6.86 and 7.23μ).[2,3]

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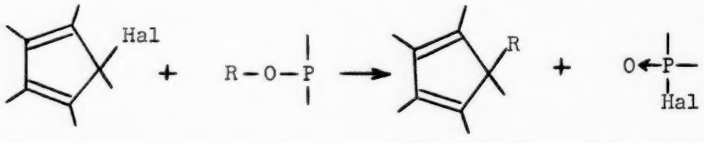
[1] G.M. Kosolapoff, Organophosphorus Compounds p. 242. John Wiley, New York (1958).

[2a] H.E. Ungnade and E.T. McBee, Chem.Rev. 58, 254 (1958); [b] C.W. Roberts, Chem. & Ind. 110 (1958).

The reaction is general and variations in both the alkyl group and the phosphorus moiety are feasible. Some of the representative II's include (R is given): methyl (b.p. 45.5°/0.28 mm, n_D^{25} 1.5465), isopropyl (b.p. 67-68°/0.42 mm, n_D^{25} 1.5397), n-butyl (b.p. 72.5°/0.28 mm, n_D^{25} 1.5270), 2-ethylhexyl (b.p. 106-107°/0.31 mm, n_D^{25} 1.5172), cyclohexyl (b.p. 95-98°/0.15 mm, n_D^{25} 1.5564), allyl (b.p. 63°/0.48 mm, n_D^{25} 1.5450), benzyl (b.p. 115-116°/0.35 mm, n_D^{25} 1.5804, m.p. 52-53°), 2-chloroethyl (b.p. 87°/0.54 mm, n_D^{25} 1.5585) and 2-methoxyethyl (b.p. 71°/0.22 mm, n_D^{25} 1.5326)[4]. The reaction takes place readily not only with phosphites but also with phosphonites, phosphinites and other types of phosphorous esters. The requirement of the alkylating agent (V) is that an alkoxy group be attached to a trivalent phosphorus atom. Thus alkoxy phosphorous anhydrides and amides are also effective alkylating agents. The essential feature of the halocyclopentadiene substrate is that it contains a chlorine or a bromine on the allylic carbon of a cyclopentadiene ring. Thus not only I, but 1,2,3,4,5-pentachlorocyclopentadiene (VI), hexabromocyclopentadiene (VII),[5] indenes and the monoalkylated products (II) themselves can effectively interact with P^{III}-esters. The reaction can thus be represented by the following generalized equation:



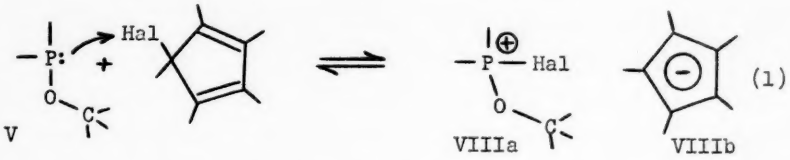
[3] L.J. Bellamy, The Infra-Red Spectra of Complex Molecules p. 13. John Wiley, New York (1959).

[4] All of the compounds listed have correct elemental analyses and spectra supporting the structures.

[5] For instance, $CH_3C_5Br_5$, m.p. 60-61°, n_D^{25} 1.6618; $C_2H_5C_5Br_5$, n_D^{25} 1.6423.[4]

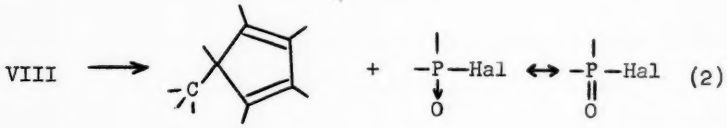
A mechanism which accomodates the results above is visualized as one consisting of two discrete steps:

1. A nucleophilic displacement on halogen by V which results in the formation of a halophosphonium cyclopentadienide (VIII):



(1)

2. A nucleophilic substitution on carbon by the cyclopentadienide ion, VIIIb:



(2)

When the substituents are alike, VIIIb can yield only one product, e.g. the 5-alkylpentahalocyclopentadiene. When the substituents are dissimilar, VIIIb can yield, in step (2), three or more isomeric products. Thus II and VI yield, on monoalkylation, three isomeric products each.[6]

The reversibility of (1) was shown by treating pure 5-methylpentachlorocyclopentadiene with a deficient amount of V necessary for a second alkylation: the recovered $CH_3C_5Cl_5$ consisted of a mixture of isomeric structures. This datum plus the formation of <u>all</u> dialkyl structures derivable through (1) and (2) argue against a concerted mechanism and support the intermediacy of VIIIb.

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[6] The further methylation of II (R=CH_3) was found to yield all three derivable dimethyltetrachlorocyclopentadienes (the 5,5-, 1,5- and 2,5-isomers). A similar pattern was recognized in dialkylations with different alkyl groups and in tri-, tetra-, etc. poly-alkylations also.

Competitive experiments with methyl, ethyl, butyl and isopropyl phosphites and mixed phosphites indicate that, unlike the Arbuzov reaction, the alkylation of I does not take place by an S_N2 step.[7] Instead, the alkyl group capable of forming the most stable carbonium ion is preferentially transferred to VIIIb. This conclusion was supported also by tert-butyl dimethylphosphinite [nuclear magnetic resonance spectrum comprises 7 peaks centered at -90.9 p.p.m. (reference 83% H_3PO_4), J = 6.1 cps] and tert-butyl diethyl phosphite (5 peaks, -135.1 p.p.m., J = 7.4 cps), which yielded, with I, 5-tert-butylpentachlorocyclopentadiene [m.p. 61.5-3.5° (from CH_3OH); λ_{max} (isooctane) 311 mμ, log ε 3.295; infrared maxima 3.38, 6.27, 6.77, 7.14, 7.29, 8.02, 11.48, 12.51, 13.92 and 14.80μ; found C, 36.6; H, 2.9; Cl, 60.7; $C_9H_9Cl_5$ requires C, 36.7; H, 3.1; Cl, 60.2%] in 70% conversion each. That a free carbonium ion, capable of isomerization, is not involved was demonstrated by the use of isobutyl phosphite, which yielded 5-isobutylpentachlorocyclopentadiene [b.p. 70° at 0.4 mm; n_D^{25} 1.5255; λ_{max} (isooctane) 311 mμ, log ε 3.257; found Cl, 60.5; $C_9H_9Cl_5$ requires Cl, 60.2%], free of the tert-butyl isomer.

Acknowledgment is expressed to Mr. Robert E. Wann and Dr. Henry C. Godt, Jr., for several of the alkylation experiments, to Dr. Bernard Katlafsky for the ultraviolet spectra, to Dr. Leo C. D. Groenweghe for the nuclear magnetic resonance spectra and to Dr. A. J. Speziale for his interest in the work and helpful discussions.

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[7] A. W. Gerrard and W. J. Green, J.Chem.Soc. 2550 (1951); B. S. R. Landauer and H. N. Rydon, Ibid. 2224 (1953).

Tetrahedron Letters No. 9, pp. 299-304, 1961. Pergamon Press Ltd. Printed in Great Britain.

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THE STRUCTURE OF QUEBRACHAMINE

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(Received 5 May 1961)

QUEBRACHAMINE is one of the alkaloids of Aspidosperma quebracho blanco Schlecht., from which also aspidospermine and yohimbine ("quebrachine") have been isolated.[1] While the structures of the two latter ones are well known, quebrachamine has received little attention and only rather recently has it been investigated chemically.[2] Quebrachamine was shown to contain an indole system from its ultraviolet spectrum,[2] and the NMR spectrum indicated alkyl substituents in the α- and β-positions but an unsubstituted indole nitrogen.[3] The lack of functional groups other than a tertiary nitrogen atom makes a specific chemical degradation difficult, and it is for this reason that only zinc dust distillation and palladium dehydrogenation have led to products for which structures have been suggested. It is reported[2] that in the former reaction 3,5-diethylpyridine, 3-methyl-5-ethylpyridine, β-methyl- and β-ethylindole, carbazole and a methylcarbazole were formed. The pyridines and the indoles were isolated in the form of their picrates but apparently no pure compounds could be

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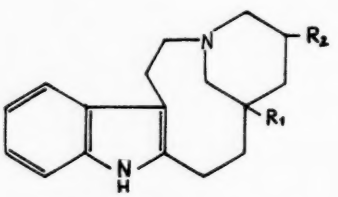
[1] O. Hesse, Liebigs Ann. 211, 249 (1882).

[2] B. Witkop, J.Amer.Chem.Soc. 79, 3193 (1957).

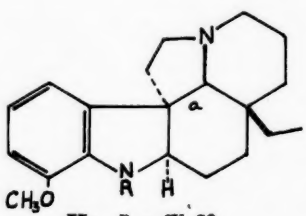
[3] L. A. Cohen, J. W. Daly, H. Kny and B. Witkop, J.Amer.Chem.Soc. 82, 2184 (1960).

obtained and the identity of these degradation products was based on melting points of mixtures and their elemental analyses.

A reinvestigation of the zinc dust distillation of quebrachamine was undertaken employing mass spectrometry for the identification of the products. Preliminary experiments on 3 mg of the alkaloid showed the formation of C_2-, C_3- and C_4-pyridines, C_1- to C_4-indoles and of a compound of molecular weight 280. Repetition of the experiment using 13 mg of quebrachamine, separation of the pyridine fraction by gas chromatography, followed by mass spectrometric determination of the structure of the products and comparison with the spectra of authentic samples showed the pyridine fraction to consist to 75% of 3-ethylpyridine; 12% of 3-methyl-5-ethylpyridine; 5% of 3-ethyl-4-methyl-pyridine; 5% of 3,5-diethylpyridine; and traces of other C_3- and C_4-pyridines. A second experiment led to the identification of 3-methylindole,[4] 2-ethylindole, 2,3-dimethylindole,[4] a methyl-ethylindole, and 2,3-diethylindole. The The formation of the 3-ethyl derivative as the major pyridine, a fact which is in contrast to earlier reports,[2] and the identification of 2,3-diethyl-indole made structure Ia an attractive working hypothesis; these two



Ia $R_1 = C_2H_5$, $R_2 = H$
Ib $R_1 = H$, $R_2 = C_2H_5$



IIa R = CH_3CO
IIb R = H

[4] Compared with the published spectra of J. H. Beynon and A. E. Williams, Appl.Spectrosc. 13, 101 (1959).

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products contain all the atoms present in quebrachamine itself if we assume that all three ethyl groups represent different parts of the original molecule. This structure, containing the carbon skeleton of aspidospermine (IIa),[5] is also a very attractive one on the basis of biogenetic considerations. For the same reason and based only on the previously reported finding that both these alkaloids give the same mixture of 3,5-diethylpyridine and 3-methyl-5-ethylpyridine on zinc dust distillation,[2] structure Ia has in the meantime been suggested by Kny and Witkop[6] and by Smith and Wrobel[7] as a possibility for quebrachamine. The formation in small quantities of 3,5-substituted pyridines requires consideration of the alternative structure Ib which would be related to ibogamine* rather than to aspidospermine. The formation of 3-ethylpyridine in such high proportions makes this structure less probable; the iboga-alkaloids yield 3-methyl-5-ethylpyridine as the major degradation product, while from aspidospermine mainly 3-ethylpyridine is obtained.**

The lack of appreciable quantities of quebrachamine prohibited a corroboration of structure Ia or Ib by specific chemical degradation, and we therefore turned our attention to a chemical correlation of quebrachamine with aspidospermine (IIa). Since we had shown previously[9] that the identity of the aliphatic carbon skeleton in differently substituted alkaloids can

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* Quebrachamine was found[8] in Stammadenia donell-smithii Woods., a plant also producing voacangin (a carbomethoxyibogaine).

** Experiments from this laboratory, to be published in the full paper.

5 J. F. D. Mills and S. C. Nyburg, Tetrahedron Letters No. 11, 1 (1959); H. Conroy, P. R. Brook and Y. Amiel, Ibid. No. 11, 4 (1959).

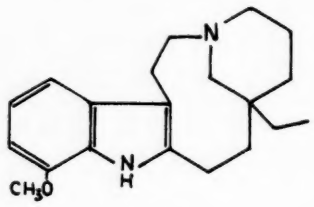
6 H. Kny and B. Witkop, J.Org.Chem. 25, 635 (1960).

7 G. F. Smith and J. T. Wrobel, J.Chem.Soc. 1463 (1960).

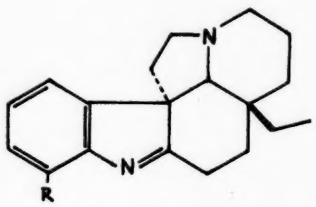
8 F. Walls, O. Collera and A. Sandoval, Tetrahedron 2, 173 (1958).

9 K. Biemann, Tetrahedron Letters No. 15, 9 (1960).

be determined by mass spectrometry, it was not necessary to remove the methoxy group in aspidospermine. It was consequently attempted to prepare III requiring cleavage of bond a in IIa accompanied by aromatization of ring B. Desacetylaspidospermine (IIb) was converted to dehydrodesacetyl-aspidospermine (IVa) by oxidation under carefully controlled conditions



III



IVa R = CH_3O
IVb R = H

(I_2 and NaOH in methanol, 3 min, room temp.). A mixture of IIb and IVa was obtained on extraction of the reaction mixture, which had been poured into water. The presence of IVa, which could not be separated from IIb, except by gas chromatography, is indicated by the ultraviolet spectrum (λ_{max} = 228, 236(sh), 255, 307 mμ; ε = 16,500, 13,700, 4900, 4500), a molecular weight of 310, and the fact that reduction with $LiAlD_4$ gives a mixture of nondeuterated and monodeuterated IIb (IVa → IIb), as shown by the mass spectrum of the product.

This mixture of IIb and IVa was reduced as such with sodium borohydride, a reaction previously used to achieve a similar conversion of a degradation product of akkuamicine into an indole derivative.[10] The product, a mixture consisting mainly of IIa and III, was separated by chromatography on alumina; the fractions containing III were combined (24% yield based on aspidospermine

[10] G. F. Smith and J. T. Wrobel, J.Chem.Soc. 792 (1960).

used) and converted to the picrate which after recrystallization from methanol had a melting point 204 to 206°, ($C_{20}H_{28}N_2O \cdot C_6H_3N_3O_7$, Found: C, 57.81; H, 5.71; N, 13.08). The free base (III) regenerated from the analytical sample of the picrate and distilled at 0.05 mm (180° air bath) was a colorless glass which could not be induced to crystallize (U.V. λ_{max} = 228, 278, 291(sh); ε = 43,600, 8020, 5680). Its mass spectrum

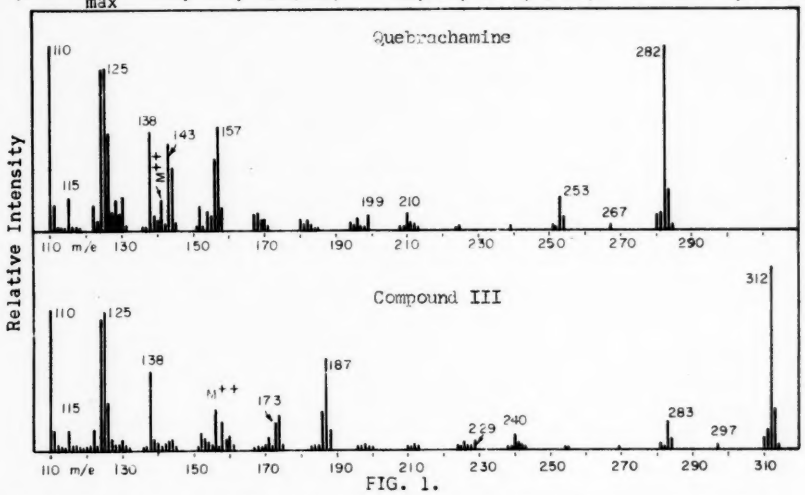


FIG. 1.

is shown in Fig. 1 along with the spectrum of quebrachamine. A careful comparison of the two spectra reveals two groups of peaks, one being of the same mass numbers in both spectra and of comparable intensities, while the other group is shifted for 30 mass numbers in the spectrum of compound III vs. the spectrum of quebrachamine. The first group consists of fragments of mass 110, 124, 125, 126, and 138 whereas the second group is at mass 143, 144, 156, 157, 196, 199, 210, 253, 267, and 282 in quebrachamine, while they are found at mass 173, 174, 186, 187, 226, 229, 240, 283, 297, and 312 in III. On the basis of these mass spectra, quebrachamine is assigned structure Ia. A methoxy derivative of Ib would be expected to exhibit a mass spectrum differing considerably from Ia, particularly in the

peaks corresponding to fragments having specifically lost the ethyl group (mass 283) or retained it (mass 110, believed to represent the piperidine ring plus ethyl). This conclusion is also corroborated by the already discussed formation of 3-ethylpyridine in the zinc dust distillation and by the fact that the mass spectrum of compound IVa is very similar to the spectrum of the zinc dust distillation product of molecular weight 280 mentioned above, with the exception of a shift for 30 mass numbers. This compound is, therefore, assigned structure IVb which implies ring closure of the quebrachamine skeleton to the one of aspidospermine, a conclusion supported by the identification of other products found in this reaction which will be discussed in the full paper.

It is of interest to note that the rotation of III ($[\alpha]_D^{25} = -103^\circ$ in dioxane) and its plain optical rotatory dispersion curve are very similar in magnitude and sign to the one of (-) quebrachamine[8] ($[\alpha]_D = -111^\circ$ in dioxane), indicating the same absolute configuration for both compounds. As methoxyquebrachamine (III) was prepared from aspidospermine, it follows that the (-) quebrachamine of Aspidosperma quebracho blanco belongs to the same configurational series at the quaternary carbon as aspidospermine while (+) quebrachamine,[8] isolated from Stammadenia-donell-smithii Woodson, is thus related to pyrifolidine,[11] the absolute configuration of which is opposite to the one of aspidospermine.

Acknowledgements - We are indebted to Dr. W.I. Taylor and Dr. B. Gilbert for samples of quebrachamine, to Dr. F.G. Smith for 2,3- and 3,5-diethylpyridine in the form of their picrates, to Dr. N. Neuss for aspidospermine, to Prof. E. Leete for 2-ethylindole, to Prof. C. Djerassi and his associates for their determination of the ORD-curve of compound III, and to the National Science Foundation for financial support (Grant G-5051).

[11] C. Djerassi, B. Gilbert, J. N. Shoolery, L. F. Johnson and K. Biemann, Experienta 17, in press (1961).

Tetrahedron Letters No. 9, pp. 305-309, 1961. Pergamon Press Ltd. Printed in Great Britain.

FURTHER EXAMPLES OF THE ADAMANTANE REARRANGEMENT

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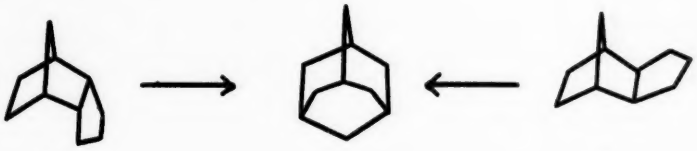
(Received 26 April 1961)

THE Lewis acid catalyzed conversion of the endo (I) and exo (II) isomers of trimethylenenorbornane (tetrahydrodicyclopentadiene) to adamantane (III)[1] represents one of the most profound rearrangements known in carbonium ion chemistry. The present investigation[2] was undertaken in the hope of obtaining insight into the mechanism of this complicated transformation. The results of the exploratory experiments reported below contribute little definitive information in this regard but they serve to demonstrate the generality of the adamantane rearrangement and to show that its extensions have preparative utility.



I III II

Besides the $C_{10}H_{16}$ isomers of adamantane, (I) and (II), we have investigated the action of $AlCl_3$ upon hydrocarbons (IV) and (V). Both formed many products as shown by gas chromatography, but no adamantane

[1] P.von R. Schleyer, J.Amer.Chem.Soc. 79, 3292 (1957); P.von R. Schleyer and M.M. Donaldson, Ibid. 82 4645 (1960).

[2] R. D. Nicholas, Ph. D. Thesis, Princeton University (1960).

was produced from either starting material. Therefore, we have adopted the working hypothesis that saturated tricyclic compounds of ten or more carbon atoms were most likely to rearrange to isomers containing the adamantane skeleton.

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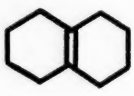

IV

V

Six methyl substituted trimethylenenorbornanes (Table 1) were prepared by standard methods[2] from the corresponding ketones.[3] Each hydrocarbon was stirred with 1/4 to 1/3 of its weight of aluminum chloride or aluminum bromide under the conditions outlined in Table 1. Work-up gave fractions boiling in the range expected for $C_{11}H_{18}$ compounds. Comparison of the physical, spectroscopic and gas chromatographic properties of authentic samples of 1-methyladamantane (VI)[4] and of 2-methyladamantane (VII)[5] with those of the $C_{11}H_{18}$ reaction product revealed the compositions recorded in Table 1. Unlike the partial conversions of I and II to adamantane (III) under similar conditions, the isomerizations of the methyltrimethylenenorbornanes to methyladamantanes was complete. None of the starting materials remained in the products.

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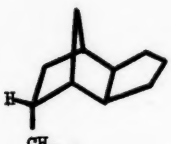
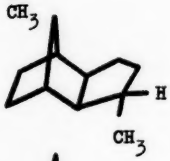
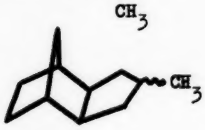
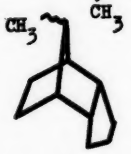
[3] J. Pirsch, Chem.Ber. 67, 1115 (1934); H. Bruson and T. W. Reiner, J.Amer.Chem.Soc. 67, 723 (1945); M. M. Donaldson, Ph. D. Thesis, Princeton University (1958); R. B. Woodward and T. J. Katz, Tetrahedron 5, 70 (1959).

[4] H. Stetter, M. Schwarz and A. Hirschhorn, Chem.Ber. 92, 1629 (1959).

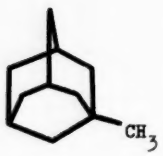
[5] P. von R. Schleyer and R. D. Nicholas, J.Amer.Chem.Soc. 83, 182 (1961).

TABLE 1

Composition of Methyladamantane Product From Isomerization of Methyltrimethylenenorbornanes

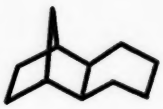
Starting material	Temp.	Time	% Yield $C_{11}H_{18}$	Composition % VI	% VII
	Room	Overnight	40	99.7	0.3
	Room	20 hr	77	92.3	7.7
	Room	Overnight	47[a]	87.3	12.7
	Room	3 Days	49[a]	84.5	15.5
	Reflux	4 hr	65	98.6	1.4
	Reflux	2 hr	-	Main	?

[a] Starting material was contaminated with olefin.



VI

VII



VIII

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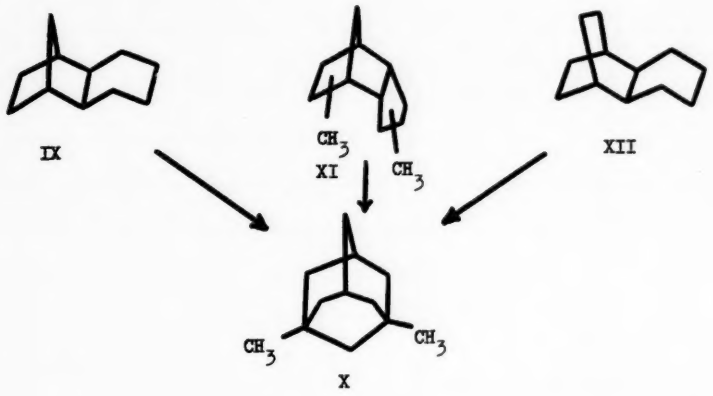
exo-Tetramethylenenorbornane (VIII) was prepared easily by hydrogenation of the butadiene-norbornadiene Diels-Alder adduct.[6] When mixed with 25% of its weight and stirred magnetically, there was an initial evolution of heat. Solid formed after a short while and the entire contents of the flask were solid the next morning. Sublimation gave a quantitative yield of substantially pure 1-methyladamantane (VI), m.p. 95.0-97.8°, shown to be free from isomers by gas chromatography (reported m.p. 103° [4]; our best value was 104.6-105.1°). The amazing facility of this transformation was further demonstrated by using cyclohexane as solvent and similar proportions of reagents; rearrangement of VIII to VI was complete in four hours under autogenous temperature. By way of contrast, no adamantane was formed from I or II with more vigorous conditions of temperature when a solvent was used.[1]

Isoprene and norbornadiene were the starting materials for the preparation of IX, the homolog of VIII. The Diels-Alder reaction gave 37% yield and the subsequent hydrogenation 83% of material, b.p. 101-103° at 15 mm, n_D^{20} 1.5049. IX was more stable than VIII to the action of $AlCl_3$; after two days at room temperature only a small change in composition was detected by gas chromatography. At 130° overnight, transformation was complete. A 74% yield of 1,3-dimethyladamantane (X) with identical infra-

[6] K. Alder, J. Münch and H. Wirtz, Liebigs Ann. 627, 47 (1959).

red spectrum to that reported[7] was obtained. The material was homogeneous.



Commercially available (Enjay Company) methylcyclopentadiene dimer, a mixture of isomers, was hydrogenated with difficulty. Stirring XI, the mixture of saturated hydrocarbons so obtained, with $AlCl_3$ on the steam bath overnight gave a 60% yield of $C_{12}H_{20}$ hydrocarbons. Analysis by gas chromatography indicated the presence of 39% X and two other unidentified components, 42% and 19%. Tetrahydrodicyclohexadiene (XII)[8] was heated with $AlCl_3$ on the steam bath. After four hours there was no further change in the product composition. Work-up gave 72% of crude material which contained 63% of X and two other unidentified components in amounts of 6% and 31%.

Further implications of these results will be discussed subsequently.

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[7] S. Landa and Z. Kamycek, Chem.Listy 52, 1150 (1958); Coll.Czech. Chem.Comm. 24, 1320 (1959).

[8] K. Alder and G. Stein, Chem.Ber. 67, 613 (1934).

Tetrahedron Letters No. 9, pp. 310-312, 1961. Pergamon Press Ltd. Printed in Great Britain.

A SIMPLIFIED ROUTE TO A KEY INTERMEDIATE IN THE TOTAL SYNTHESIS OF α-ONOCERIN[1]

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Daniel Sieff Research Institute, Weizmann

Institute of Science, Rehovoth, Israel

(Received 1 May 1961)

dl-1,1,10β-Trimethyl-trans-decal-2β-ol-6-one-5-acetic acid (VI) is a key intermediate in the total synthesis of α-onocerin of Stork et al.,[2] since it can be converted to this naturally occurring triterpene by successive resolution, electrolytic coupling and transformation of the carbonyl to methylene groupings.[2] Very recently Church et al.[3] have described an alternative synthesis of the acid (VI) by a route which proceeds from the keto-benzoate (I) first prepared in our laboratories.[4] This latter publication prompts us now to report a new and much more direct method for carrying out the conversion of (I) to (VI). Our synthesis of (VI) moreover involves fewer steps than that of Stork et al.[2] and is therefore the shortest one available.

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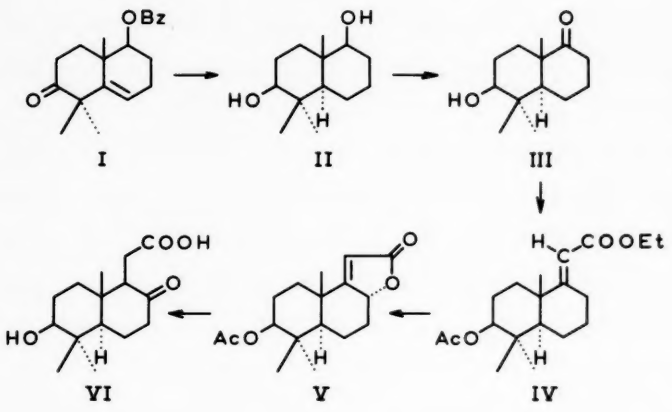
[1] For previous work in this series see F. Sondheimer and M. Gibson, Bull.Res.Counc.Israel 9A, 204 (1960).

[2] G. Stork, J. E. Davies and A. Meisels, J.Amer.Chem.Soc. 81, 5516 (1959).

[3] R. F. Church, R. E. Ireland and J. A. Marshall, Tetrahedron Letters No. 1, 34 (1961).

[4] F. Sondheimer and D. Elad, J.Amer.Chem.Soc. 79, 5542 (1957).



The keto-benzoate (I)[4] on saponification and subsequent hydrogenation of the resulting keto-alcohol[5,6] in acetic acid over platinum yielded 85%[7] of the saturated diol (II) (m.p. 180-182°; Found: C, 73.33; H, 11.26). Partial oxidation with 1.2 equivalents of chromium trioxide in pyridine gave the known keto-alcohol (III) (m.p. 72-74°)[5,8,9,10] in 45% yield (based on unrecovered diol); reduction with lithium aluminum hydride of the other oxidation products then brought the yield of (III) to 80%.[11]

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5 F. Sondheimer and D. Elad, J.Amer.Chem.Soc. 80, 1967 (1958).

6 J. D. Cocker and T. G. Halsall, J.Chem.Soc. 3441 (1957).

7 Yields are given to the nearest 5%.

8 J. Kalvoda and H. Loeffel, Helv.Chim.Acta 40, 2340 (1957).

9 B. Gaspert, T. G. Halsall and D. Willis, J.Chem.Soc. 624 (1958).

10 N. B. Haynes and C. J. Timmons, Proc.Chem.Soc. 345 (1958).

11 The present 3-step method for transforming (I) to (III) is considerably simpler than the one described by us previously.[5]

Acetylation of (III), followed by condensation with lithium ethoxyacetylide in ether and then treatment with 5% methanolic sulfuric acid at room temperature, afforded 55% of the αβ-unsaturated ester (IV) [m.p. 85-86° and 99-100° (polymorphic forms); λ_{max}^{EtOH} 221 m (ε 13,400); infrared bands (KBr) at 1739, 1718 and 1640 cm^{-1}; Found: C, 70.74; H, 9.37]. Oxidation with selenium dioxide in boiling acetic acid produced the αβ-unsaturated γ-lactone (V) [m.p. 129-130°; λ_{max}^{EtOH} 215 m (ε 11,900); infrared bands (KBr) at 1757, 1736 and 1640 cm^{-1}; Found: C, 69.67; H, 8.12] in 75% yield. Finally, treatment with 20% potassium hydroxide in boiling aqueous ethylene glycol led to 55% of the acid (VI) (m.p. 185-186°) which proved to be identical (mixture m.p., infrared comparison) with a sample kindly provided by Dr. A. Meisels. The corresponding methyl ester (m.p. 110-111°) likewise was identified with an authentic sample.

Tetrahedron Letters No. 10, pp. 313-316, 1961. Pergamon Press Ltd. Printed in Great Britain.

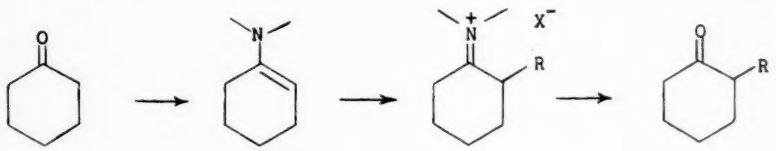
THE ALKYLATION OF ENAMINES FROM α,β-UNSATURATED KETONES[1]

Gilbert Stork and George Birnbaum

Chandler Laboratories, Columbia University, New York 27, New York

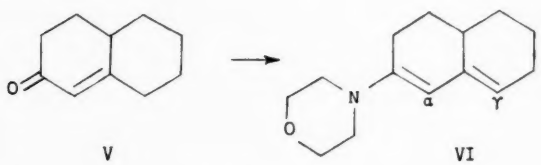
(Received 24 May 1961)

WE have extended our studies on the introduction of alkyl groups in the α-position of carbonyl compounds via initial transformation into enamines[2] (cf. I - II - III) to a study of the position of alkylation in the enamines of α,β-unsaturated ketones.



I II III IV

There are obviously three a priori possibilities which we can illustrate with the enamine derived from the unsaturated ketone $\Delta^{1(9)}$octalone-2 and morpholine:



V VI

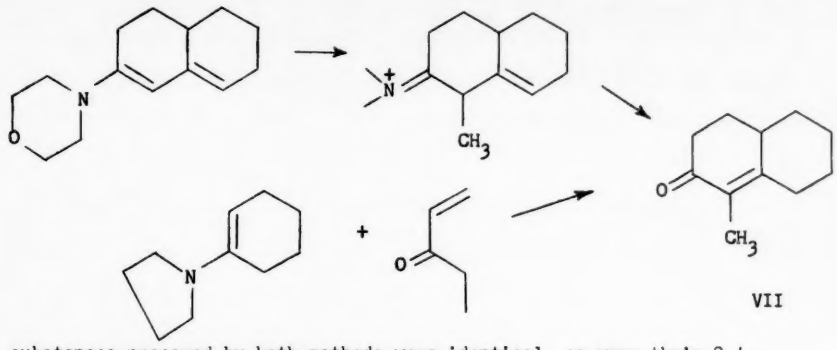
[1] cf. G. Birnbaum, Ph.D. Thesis, Columbia University, New York (1961).

[2] G. Stork, R. Terrell and J. Szmuszkovicz, J.Amer.Chem.Soc. 76, 2029 (1954).

Reaction with an alkylating agent could take place on the nitrogen with formation of a quaternary salt; or C-alkylation could result with the formation of either α- or γ-alkylated products. That introduction of alkyl groups on carbon takes place at the α position was demonstrated as follows: The morpholine enamine of $\Delta^{1(9)}$octalone-2 was prepared by refluxing a solution of 30 g of $\Delta^{1(9)}$octalone-2 (V) and three equivalents of morpholine in 300 ml of toluene for 36 hr. Distillation gave the morpholine enamine (VI) in 75% yield, (b.p. 135-137°/0.3 mm); $\lambda_{max}^{CHCl_3}$ 6.24 $\lambda_{max}^{Et_2O}$ 270 mμ, ε 13,000. (Found: C, 76.36; H, 9.59. Calc. for $C_{14}H_{21}ON$: C, 76.66; H, 9.65). In the same general way the pyrrolidine and hexamethylene imine enamines were also prepared but did not prove as satisfactory.

Alkylation of VI with methyl iodide was carried out by refluxing for 20 hr a solution of 5 g of the enamine in 50 ml of dry dioxane with an equimolar amount of methyl iodide. A solution of 1.5 g of sodium acetate in 3 ml of acetic acid and 3 ml of water was then added and the mixture was refluxed for 4 hr to hydrolyze the enamine. Extraction with ether followed by washing with 5% hydrochloric acid, saturated bicarbonate, and finally saturated salt solution gave, after removal of solvent, a mixture of α,β- and β,γ-unsaturated ketones (by infrared) which was isomerized to the conjugated form by stirring overnight under nitrogen with 4% methanolic potassium hydroxide. The resulting ketonic material was shown to contain in addition to some unreacted ketone V the product of alkylation on the α-carbon atom: 1-methyl $\Delta^{1(9)}$octalone-2 (VII). No other substance could be detected by careful gas chromatography on a column of Craig polyester succinate. The identity of the ketone was established by direct comparison with authentic VII made by addition of ethyl vinyl ketone to the pyrrolidine enamine of cyclohexanone.[3] The infrared and ultraviolet spectra of the

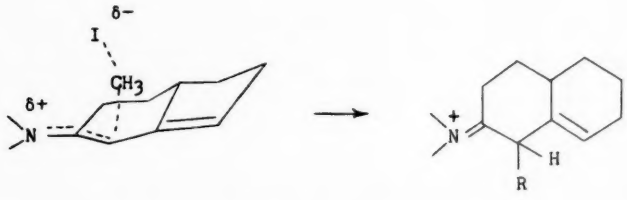
[3] G. Stork and H. K. Landesman, J.Amer.Chem.Soc. 78, 5128 (1956).



VII

substances prepared by both methods were identical, as were their 2,4-dinitrophenylhydrazones, m.p. 177.5-178.5°.

It is thus clear that carbon alkylation of the enamine of an α,β-unsaturated ketone results in alkylation at the same position as alkylation of the metal enolate ion[4] (except, of course, that, as usual, monoalkylation results via the enamine route). This result suggests that an important factor may be the lowering of the energy of the transition state resulting from release of halide anion in close proximity to the positively charged ammonium ion:



It should also be noted that other electrophilic reagents appear to react in similar fashion with enamines:[5] Reaction with perchloryl fluoride

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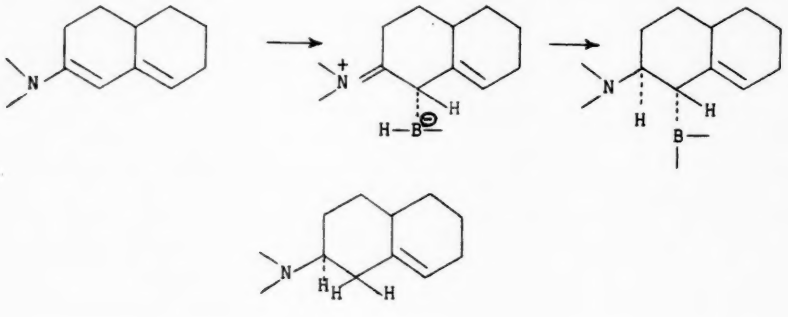
[4] cf. J. M. Conia, Bull.Soc.Chim. 690 (1954).

[5] A recent use of the enamine alkylation reaction for the α-alkylation of an unsaturated ketone has been reported by L. Velluz, G. Nomine, R. Bucourt, A. Pierdet and P. Dufay, Tetrahedron Letters No. 3, 127 (1961).

attacks the α-position[6] and the reduction of enamines of α,β-unsaturated ketones with sodium borohydride[7] can be interpreted similarly assuming that the reducing agent is diborane:



[6] S. Nakanishi, K. Morita and E. V. Jensen, J.Amer.Chem.Soc. 81, 5259 (1959).

[7] W. S. Johnson, V. J. Bauer and R. W. Franck, Tetrahedron Letters No. 2, 72 (1961).

Tetrahedron Letters No. 10, pp. 317-320, 1961. Pergamon Press Ltd. Printed in Great Britain.

COMMENTS ON THE STRUCTURE OF QUASSIN

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and

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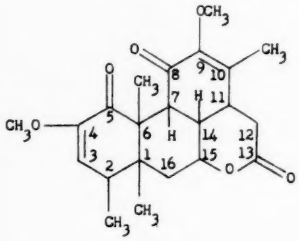
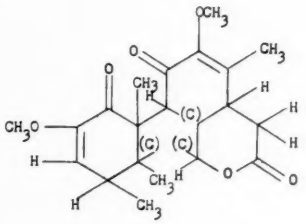
Wellington, New Zealand

(Received 10 March 1961; in revised form 15 May 1961)

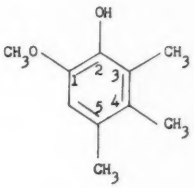
VALENTA et al.[2] have recently suggested the structure I for quassin, one of the two closely related diterpenoid compounds obtained from Quassin amara Linn, on the basis of partial structure II which they established by both chemical and nuclear magnetic resonance (NMR) evidence.



I



II



III

[1] Present address: Chemistry Department, University of Queensland, Brisbane, Australia.

[2] Z. Valenta, A. H. Gray, S. Papadopoulos and C. Podesva, Tetrahedron Letters No. 20, 25 (1960).

Unequivocal evidence was not presented for the siting of a methyl group at C_1. While 3,4,5-trimethylguaiacol III can be obtained by dehydrogenation of neoquassin,[3] the C_4 methyl of this aromatic compound could well be derived from the C_{16} atom of quassin and does not provide proof of the presence of an angular C_1 methyl group in the parent compound. For this reason, and for others detailed below, we consider that the formula IV is at the present stage an acceptable alternative for the structure of quassin.

In agreement with the data of the Canadian group[2] we find that the NMR spectrum[4] of quassin shows methyl absorption at 8.13, 8.45, 8.81 (doublet) and 8.89τ. These peaks can be assigned to an allylic methyl group, an angular methyl group adjacent to a carbonyl group, a methyl group attached to a socondary carbon atom and a methyl group attached to a teriary carbon atom respectively. Such assignments are in agreement with both structures I and IV. Further evidence has been presented to establish the position of three of these methyl groups at C_2, C_6 and C_{10}.[2]

In the NMR spectra of quassin, neoquassin, anhydroneoquassin and deoxoquassin, which are related as shown in Fig. 1, we have been able to assign the various bands to a proton or protons in the molecule with considerable confidence and thus to account for the resonance position of each proton in the four compounds studied. In each case a sharp singlet of area equivalent to one proton occurs in the region 6.80-7.05τ, and this peak is assigned to the proton on C_7. Besides occupying an angular position

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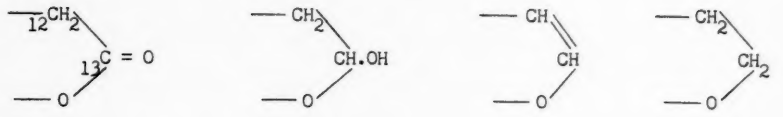
[3] R. J. S. Beer, D. B. G. Jaquiss, A. Robertson and W. E. Savige, J.Chem.Soc. 3672 (1954).

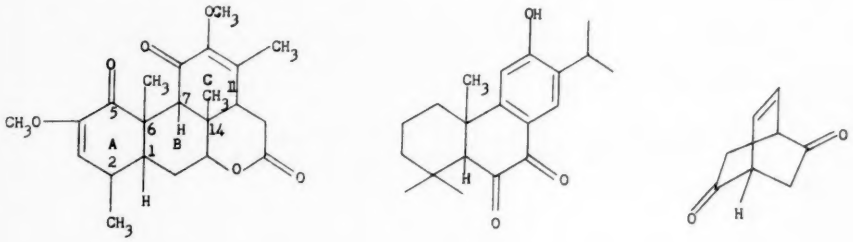
[4] All spectra were measured at 60 mc in deuterochloroform solution using tetramethylsilane as an internal reference. Chemical shifts are reported as τ values. [G. V. Tiers J.Phys.Chem. 62, 1151 (1958).]



quassin neoquassin anhydroneoquassin deoxoquassin

FIG. 1.

between rings B and C, this proton is also alpha to the carbonyl group at C_8, and it should resonate at a lower τ value than a normal tertiary proton.[5] The proton under discussion would also be expected, because of the spatial proximity of the C_5 carbonyl group, to resonate at a lower τ value than the angular proton in xanthoperol V (7.36τ),[6] but at a higher value than the bridgehead protons in compound VI (6.73τ),[7] as these latter protons are also allylic to a double bond. The C_7 proton resonance of quassin and its derivatives thus occur within the predicted range.



IV V VI

The unsplit nature of the C_7 proton resonance can be explained in

[5] L. M. Jackman, Applications of Nuclear Magnetic Resonance Spectroscopy in Organic Chemistry p. 57. Pergamon Press, London (1959).

[6] J. B. Bredenburg and J. N. Shoolery, Acta Chem.Scand. 14, 556 (1960).

[7] C. A. Grob and A. Weiss, Helv.Chem.Acta 43, 1390 (1960).

two ways. Firstly it is possible that a proton on an adjacent carbon may be sterically situated such that the coupling constant between the adjacent protons is zero. From the work of Conroy[8] on rigid caged systems, a coupling constant of zero between nonequivalent vicinal tertiary protons requires that the dihedral angle between these protons be approximately 90°, and hence that the rings B and C in quassin and its derivatives be cis fused. At present no information is available as to the stereochemistry of the ring system.

The second, and in our opinion the more likely explanation, as to why in each of the four compounds studied the C_7 proton remains unsplit is that there is no proton on the adjacent carbon atom. As no information is available concerning the degree of substitution at C_{14} and as no proof for the siting of a methyl group at C_1 has been presented, it is considered that structure IV for quassin is at least as compatible with the available evidence as is structure I.

Further work is in progress to rigorously prove the structure and stereochemistry of quassin.

Acknowledgements - We are indebted to Professor D. S. Tarbell, University of Rochester, for the NMR spectra. One of us (A.D.W.) acknowledges the award of a Victoria University of Wellington Research Scholarship.

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[8] H. Conroy, Advances in Organic Chemistry: Methods and Results Vol. 2, p. 311. Interscience, New York (1960).

Tetrahedron Letters No. 10, pp. 321-324, 1961. Pergamon Press Ltd. Printed in Great Britain.

ISOLEMENT DE DÉRIVÉS DIPHÉNYLIQUES PAR FUSION ALCALINE DE LA LUNARINE[1]

Peter Bladon,[2] Marcel Chaigneau,[3] Maurice-Marie Janot,[4] Jean Le Men,[4] Pierre Potier[4] et A. Melera[5]

(Received 10 April 1961; in revised form 18 May 1961)

DANS une publication anterieure,[6] nous avons relaté la formation de spermidine par fusion alcaline de la lunarine ($C_{25}H_{31}O_4N_3$). A côté de ce produit basique, il se forme au cours de la même opération un mélange de produits phénoliques et acides[7] qui est retenu par le milieu alcalin. Ce mélange peut être séparé en:

(a) fraction phénolique volatile, constituée surtout par du phénol, de l'o-crésol et plusieurs autres homologues supérieurs identifiés par chromatographie en phase gazeuse.

(b) fraction phénolique non volatile dont la pyrolyse sur poudre de zinc fournit du diphényle caractérisé par son spectre ultra-violet.

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[1] Cette publication est le 3ème mémoire de la série "The Chemistry of Lunaria Alkaloids" (Glasgow) et le 5ème mémoire de la série "Alcaloides du Lunaria biennis Moench" (Paris).

[2] Chemistry Department, Royal College of Science and Technology Glasgow.

[3] Laboratoire des Gaz du C.N.R.S., 4 av. de l'Observatoire, Paris.

[4] Laboratoire de Pharmacie Galénique, Faculté de Pharmacie, Paris.

[5] Laboratoire de Varian A. G. Zürich.

[6] P. Potier, J. Le Men, M.-M. Janot et P. Bladon, Tetrahedron Letters No. 18, 36 (1960).

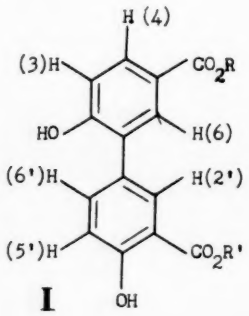
[7] P. Potier et J. Le Men, Bull.Soc.Chim. 456 (1959).

(c) un mélange d'acides acétique et propionique ainsi que des quantités beaucoup plus faibles et décroissantes d'acides isobutyrique, butyrique, isovalérianique et valérianique identifiés par chromatographie en phase gazeuse; et enfin:

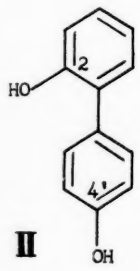
(d) plusieurs acides non volatile.

Le principal acide de ce dernier groupe est biacide, il répond à la formule brute $C_{14}H_{10}O_6$. Il doit s'agir du dihydroxy 2-4' diphényl 5-3' dioique (I; R = R' = H) et ce, pour les raisons suivantes:

Chauffé sous vide aux alentours de son point de fusion (265°) cet acide se décompose en libérant quantitativement deux molécules de gaz carbonique et donne naissance à un composé connu;[8] le dihydroxy 2-4' diphényle (II).



I



II

Le méthanol saturé de gaz chlorhydric, à froid, transforme ce diacide en son monoester méthylique (I; R=CH_3, R'=H); le même réactif, à reflux, le transforme en son diester méthylique (I; R=R'=CH_3). Le diacide et ses esters fournissent une intense coloration violette avec le chlorure ferrique ainsi que le font les acides et esters o-phénols.

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[8] Fichter et Brunner, Bull.Soc.Chim. 19, 286 (1916); Finzi et Mangini, Gazz.Chim.Ital. 62, 1193 (1933); Schmidt, Schultz et Strasser, Liebigs Ann. 207, 357 (1881).

Par contre, seul l'acide libre (I; R=R'=H) fournit, lorsqu'il est soumis au test de Gibbs[9] (réaction avec le dérivé N- chloré de la dichloro-iminoquinone) une coloration bleue accompagnée d'un dégagement de gaz carbonique. Son monoester et son diester donnent tous deux des colorations brunes. Ceci indique que les positions en para des deux groupes hydroxyles sont substituées et que l'une au moins l'est par un groupe carboxyle.

Le spectre de résonance magnétique nucléaire[10] du diester méthylique (I; R=R'=CH_3) est en accord avec la formule proposée; en particulier, on y trouve: -un pic à τ = -0,9 qui indique la présence d'un groupe phénolique fortement chélaté (cf. τ =-0,58 pour le salicylate de méthyle[11]).

-un pic à τ = 4,17, du au second groupe phénolique non chélaté.

-une série de quatorze pics, situés dans la région comprise entre τ = 2,1 et τ = 3,35, attribués aux six atomes d'hydrogène portés par le système aromatique; parmi ces pics se trouvent deux doublets qui se recouvrent, situés à τ = 2,80 et 3,07 et dus à deux atomes d'hydrogène non mutuellement couplés (3 et 5'), mais couplés chacun à un seul atome d'hydrogène en ortho (4 et 6'); on peut encore noter un "quartet" (τ = 2,41) caractéristique d'un atome d'hydrogène (4 ou 6') couplé à deux autres atomes d'hydrogène, l'un en ortho, l'autre en méta.

Le reste du spectre est complexe mais il exclut néanmoins la possibilité d'une substitution benzénique 1, 2, 3 ou 1, 3, 5.

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[9] Gibbs. J.Biol.Chem. 72, 649 (1927); Davidson, Kesne et Nolan, Proc.Roy.Soc. (Dublin) 23, 43 (1942-1944).

[10] Déterminé à 60 Mc/sec dans le chloroforme deutéré et avec un étalon interne de tétraméthylsilanne, l'échelle τ, utilisée ici, est définie par G. V. D. Tiers, J.Phys.Chem. 62, 1151 (1958).

[11] L. M. Jackman, Applications of Nuclear Magnetic Resonance Spectroscopy in Organic Chemistry p. 71. Pergamon Press, London (1959).

D'une part la structure probable (I; R=R'=H) de l'acide, d'autre part l'identification antérieure[1] de la spermidine dans les produits que fournit la fusion alcaline de la lunarine, permettent de fixer l'enchaînement de vingt et un atomes de carbone sur les vingt-cinq que comporte cette molécule.

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Tetrahedron Letters No. 10, pp. 325-332, 1961. Pergamon Press Ltd. Printed in Great Britain.

ESTABLISHMENT OF THE CORRELATION OF OBACUNONE AND LIMONIN[1]

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Minamiogimachi, Kitaku, Osaka, Japan

(Received 26 April 1961; in revised form 27 May 1961)

ARIGONI, Barton, Corey, Jeger, and collaborators established the complete structure I for limonin. They also proposed the formula II as the plausible and biogenetically attractive one for obacunone.[2] Kubota, Kamikawa, Tokoroyama, and Matsuura proposed the partial structure III on the basis of the degradation reaction of obacunone.[1,3-6] Recently, the partial structure IV for obacunone has been provided by Barton and collaborators. These workers have also suggested the stereochemical structure V by assuming that obacunone is related, stereochemically as well as constitutionally, to

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[1] For previous work see: T.Matsuura, T.Kamikawa and T.Kubota, Tetrahedron 12, 269 (1961).

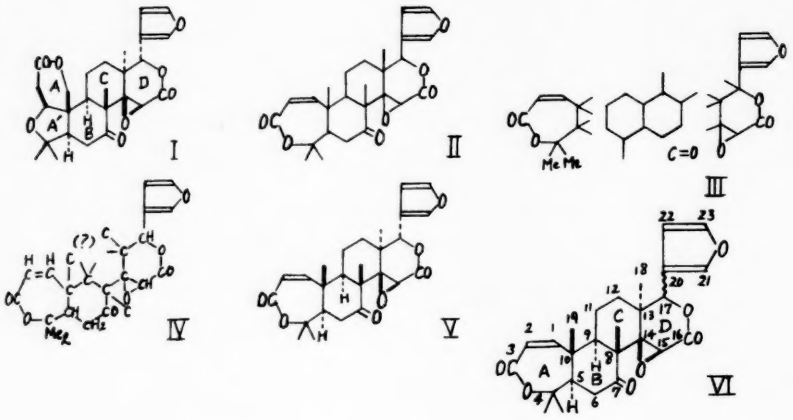
[2] D.Arigoni, D.H.R.Barton, E.J.Corey, O.Jeger and collaborators, Experimentia 16, 41 (1960).

[3] T.Kubota, T.Kamikawa, T.Tokoroyama and T.Matsuura, Tetrahedron Letters No. 8, 1 (1960).

[4] T.Kubota and T.Tokoroyama, Chem. & Ind. 298 (1957); also see T.Tokoroyama, J.Chem.Soc.Japan 79, 319 (1958).

[5] T.Tokoroyama, T.Kamikawa and T.Kubota, Bull.Chem.Soc.Japan 34, 131 (1961).

[6] T.Kamikawa and T.Kubota, Tetrahedron 12, 262 (1961).



limonin.[7] We now wish to report that the stereochemical structure VI has been established for obacunone by the correlation of obacunone and limonin via a degradation product and by the incidental chemical evidences.

When obacunoic acid (VII) was treated with barium hydroxide for a shorter time than in process of the preparation of isoobacunoic acid (VIII: R=H) from obacunoic acid, it afforded a new isomer of obacunoic acid, epi-isoobacunoic acid (IX: R=H), $C_{26}H_{32}O_8$,* m.p. 270-271° dec. (λ_{max}^{EtOH} 209 mμ (ε 5900); ν_{max}** 3200, 1738, 1712, 1700 cm^{-1}), which lacked the α,β-unsaturated acid group and also the hydroxyl group like isoobacunoic acid. Epi-isoobacunoic acid could be converted to isoobacunoic acid on treatment with barium hydroxide for a longer time. This result and the other properties of epi-isoobacunoic acid show that this acid is an epimer of

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* All analytical data were satisfactory to the calculated values.

** All infra-red spectra were taken in Nujol.

7 D.H.R.Barton, S.K.Pradham, S.Sternbell and J.F.Templeton, J.Chem.Soc. 255 (1961).

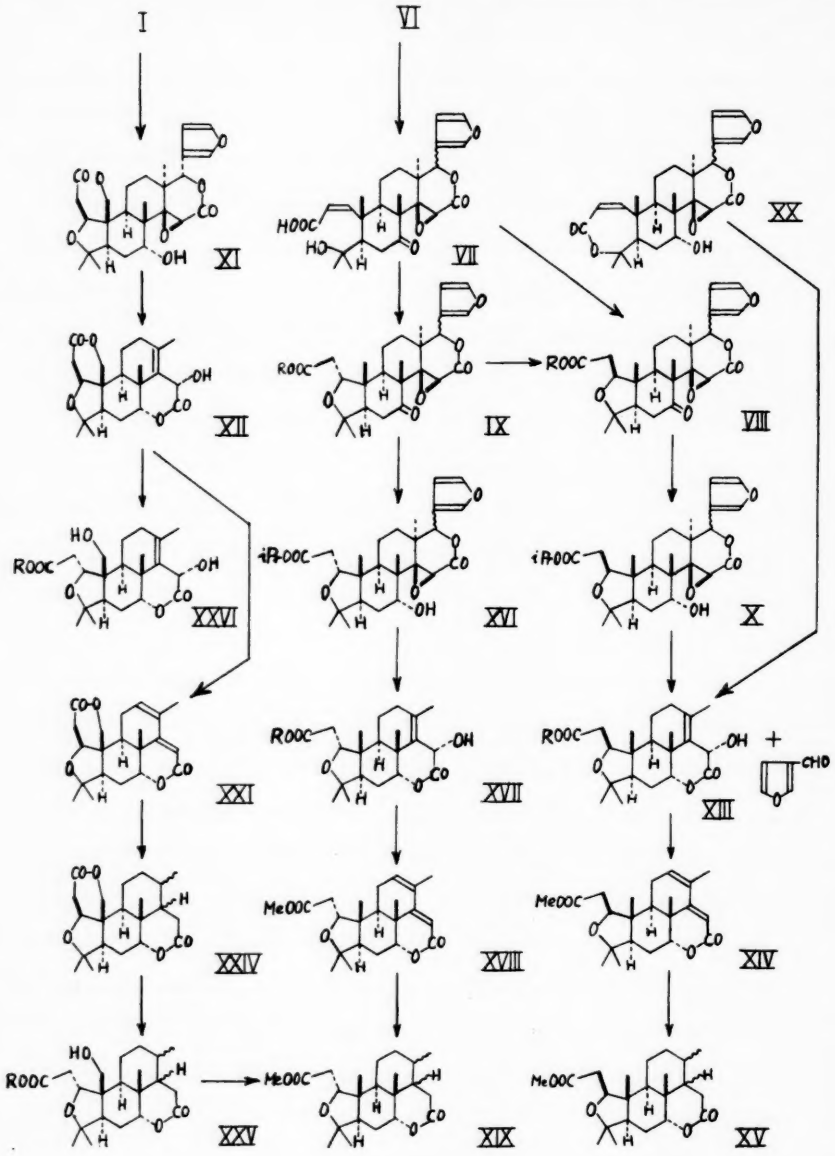
isoobacunoic acid at the C_1-position.

Meerwein-Ponndorf reduction of methyl isoobacunoate (VIII; R=CH_3), $C_{27}H_{34}O_8.CH_3CO_2H$, m.p. 116-119°, afforded isopropyl isoobacunolate (X), $C_{29}H_{40}O_8$, m.p. 236-237°, as the major product. Treatment of X with sodium hydroxide under the condition needed to transform limonol (XI) to meroolimonol (XII)[8] gave meroobacunolic acid (XIII; R=H), $C_{21}H_{30}O_6.CH_3OH$, m.p. 195-196° (ν_{max} 3400-3360, 2720-2400, 1723, 1710, 1663 cm^{-1}), characterized as the monomethyl ester, $C_{22}H_{32}O_6$, m.p. 194-195° (λ_{max}^{EtOH} 226.5 mμ (ε 2950); λ_{min}^{EtOH} 218 mμ (ε 2740); ν_{max} 3400, 1732 cm^{-1}), and monoacetate, $C_{23}H_{32}O_7.CH_3OH$, m.p. 140-142° dec. Methyl meroobacunolate (XIII; R=CH_3) was dehydrated with phosphorous oxychloride and pyridine to give methyl anydromeroobacunolate (XIV), $C_{22}H_{30}O_5$, m.p. 174-175° (λ_{max}^{EtOH} 277 mμ (ε 13,400); ν_{max} 1730, 1713, 1645, 1612, 818 cm^{-1}), which, on catalytic hydrogenation, gave methyl tetrahydroanhydromeroobacunolate (XV), $C_{22}H_{34}O_5$, m.p. 104-105° (ν_{max} 1730, 1717 cm^{-1}).

Methyl epi-isoobacunoate (IX; R=CH_3), a amorphous solid, was subjected to the above series of reactions. Meerwein-Ponndorf reduction afforded exclusively isopropyl epi-isoobacunolate (XVI), $C_{29}H_{40}O_8$, m.p. 187-188° (ν_{max} 3500, 1730, 1165 cm^{-1}), which, on treatment with sodium hydroxide, gave an isomer of meroobacunolic acid, epi-meroobacunolic acid (XVII; R=H), $C_{21}H_{30}O_6.H_2O$, m.p. 243-244° (ν_{max} 3480, 2700-2500, 1738, 1720, 1675 cm^{-1}). This acid was characterized as the monomethyl ester, $C_{22}H_{32}O_6$, m.p. 145-147° (λ_{max}^{EtOH} 226.5 mμ (ε 2990); λ_{min}^{EtOH} 218 mμ (ε 2740); ν_{max} 3480, 1738, 1722 cm^{-1}), and monoacetate, $C_{23}H_{32}O_7.H_2O$, m.p. 224-226°.

Dehydration of methyl epi-meroobacunolate (XVII; R=CH_3) afforded methyl anhydro-epi-meroobacunolate (XVIII), m.p. 192-194° (λ_{max}^{EtOH} 276 mμ

[8] A.Melera, K.Schaffner, D.Arigoni and O.Jeger, Helv.Chim.Acta 40, 1427 (1957).


I
VI
XI
VII
XX
XII
IX
VIII
XXVI
XVI
X
XXI
XVII
XIII
XXIV
XVIII
XIV
XXV
XIX
XV

(ε 11,900); ν_{max} 1730, 1700, 1633, 1600, 790 cm^{-1}), which, on catalytic hydrogenation, gave methyl tetrahydroanhydro-epi-meroobacunolate (XIX), $C_{22}H_{34}O_5$, m.p. 193-194° [ν_{max} 1730, 1715 cm^{-1}, $[\alpha]_D$ + 30° (C, 0.90; EtOH)].

On the other hand, sodium brohydride reduction of obacunone afforded two isomeric alcohol, obacunol (XX), $C_{26}H_{32}O_7 \cdot C_2H_5OH$, m.p. 248-250° ($\nu_{max}$ 3640-3560, 1724, 1690, 1066 cm^{-1}), as the major product, and iso-obacunol, $C_{26}H_{32}O_7 . 2CH_3OH$, m.p. 134-137° dec. ($\nu_{max}$ 3640-3440, 1730, 1690, 1018, 1040 cm^{-1}), as the minor product. Obacunol was characterized as the monoacetate, $C_{28}H_{34}O_8$, $1/2CH_3OH$, m.p. 151-153° dec. (ν_{max} 1730, 1715, 1690, 1220 cm^{-1}), and on chromium trioxide oxidation gave obacunone. Isoobacunol was also characterized as the monoacetate, $C_{28}H_{34}O_8$, m.p. 212-214° (ν_{max} 1738, 1700, 1680, 1240, 1032 cm^{-1}). At present there is not sufficient data for the correlation among these two alcohols and α- and β-obacunol obtained by potassium borohydride reduction[9] of obacunone. Meroobacunolic acid (XIII; R=H) and furan-3-aldehyde, (2,4-dinitrophenyl-hydrazone, $C_{11}H_8O_5N_4$, m.p. 231-233°*) were isolated on treatment of obacunol (XX) with sodium hydroxide. Furthermore meroobacunolic acid and epi-meroobacunolic acid were also obtained by the Meerwein-Ponndorf reduction of obacunone followed by alkali treatment of the amorphous reduction product

The ultra-violet spectra of the methyl esters of meroobacunolic acid and epi-meroobacunolic acid were superimposable on that of merolimonol (XII) and the absorption maxima of the anhydro derivatives of both methyl esters, XIV and XVIII, were also identical with that of anhydromerolimonol (XXI). From these results, we can now formulate meroobacunolic acid and epi-meroobacunolic acid as the partial structure XXII, consequently

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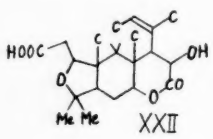
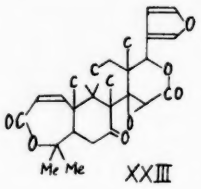
* The 2,4-dinitrophenylhydrazone was identical with an authentic sample which was kindly supplied by Dr. S.Kusumoto.

9 F.M.Dean and T.A.Geissman, J.Org.Chem. 23, 596 (1958).

obacunone as the structure XXIII. The fact that IX and XVI are obtained as



XXII



XXIII

the major product of the Meerwein-Ponndorf reduction and the inspection of the C-O stretching band[10] of obacunol (XX) and its acetate led us to the conclusion that the C_7-hydroxyl groups of meroobacunolic acid and of epi-meroobacunolic acid have axial configuration and therefore XIII (R=H) and XVII (R=H) must be epimeric at the C_1-position.

After failures of several attempts to inter-relate obacunone and limonin, we have succeeded in the derivation of limonin to methyl tetrahydroanhydro-epi-meroobacunolate (XIX). Tetrahydroanhydromerolimonol (XXIV) obtained from merolimonol (XII) *via* anhydromerolimonol (XXI) according to the method of Melera *et al.*,[8] was hydrolysed with barium hydroxide under drastic conditions to give a lactonic hydroxy-acid (XXV; R=R'=H), $C_{21}H_{32}O_6$, m.p. 265° dec. (ν_{max} 3470, 3180-2450, 1730, 1700 cm^{-1}). In this acid the lactone ring A was opened irreversibly and we assigned the structure XXV (R=R'=H), having the acetic acid side-chain with α-configuration at the C_1-position, comparable to the acid XXVI (R=H)[2] obtained from merolimonol. In our experiment, the acid (XXVI;R=H) was obtained as a crystalline form, $C_{21}H_{30}O_7 \cdot 1.5H_2O$, m.p. 243-244° dec., which was characterized as the monomethyl ester (XXVI; R=CH_3), $C_{22}H_{32}O_7$, m.p. 228-230°.

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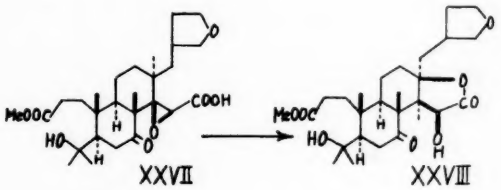
[10] E.A.Braude and E.S.Waight in W.Klyne, Progress in Stereochemistry Vol. I, p. 166. Butterworths,London (1954).

The lactonic hydroxy-acid (XXV; R=R'=H) was converted to the monomethyl ester (XXV; R=CH_3, R-=H), $C_{22}H_{34}O_6$, m.p. 205° (ν_{max} 3530, 1733, 1715 cm^{-1}). After several attempts to remove the hydroxyl group of this ester had been failed, the ester was converted to the mesylate (XXV; R=CH_3, R'=CH_3SO_2), $C_{23}H_{36}O_8S$, m.p. 209-210° (ν_{max} 1733, 1353, 1173, 983 cm^{-1}). Treatment of the mesylate with sodium iodide at 180° afforded an acidic product which, on methylation with diazomethan followed by treatment with zinc and acetic acid, gave a crystalline product, m.p. 194-195°, ($[\alpha]_D$ + 33° (C, 1.09; EtOH)). This product was identical with methyl tetrahydroanhydro-epi-meroobacunolate (XIX) as shown by comparison of infra-red spectrum (in both Nujol and chloroform) and in the mixture melting point determination. Anomalous formation of the acidic product in this reaction can be explained by the known type of hydrolysis of esters with metal halides.[11]

The derivation of XIX from limonin has regorously established the structure II for obacunone and also the same configurations at C_5-, C_8-, C_9- and C_{10}-positions as in limonin. Among four remaining asymmetric carbon atoms, the configurations at the C_{13}-, C_{14}- and C_{15}-positions have been deduced as follows. Barton and collaborators[7] found that treatment of methyl hydrogen octahydroobacunoninate (XXVII) with acid afforded the acidic product (XXVIII), analogous to the product of the acid-catalysed rearrangement of hexahydrolominic acid, and concluded that the CD ring



[11] F.Elsinger, J.Schreiber and A.Eschenmoser, Helv.Chim.Acta 43, 113 (1960) and cited references.

fusion of obacunone must be trans.[12] Furthermore, we can conclude that the 14, 15-epoxy group in obacunone probably has the β-configuration, since the back side attack of the 7-α-hydroxyl group to the C_{14}-position of the epoxy group of isopropyl epi-isoobacunolate (XVI) is required in the transformation of XVI to epi-meroobacunolic acid (XVII; R=H), comparable to the transformation of limonol (XI) to merolimonol (XII).[2,12]

We can now conclusively formulate obacunone as the sterochemical structure VI. Although the stereochemistry of the C_{17}-position can not be rigidly designated by chemical evidences, we assume that the β-furyl group has the α-configuration as shown in the structure V. We hope to provide a final solution to this problem in a further communication.

Our result indicates that the side-chains at the C_1-position of isoobacunoic acid (VIII; R=H) and epi-isoobacunoic acid (IX; R=H) have, respectively the β- and α-configuration. It is concluded that, in a series of obacunone derivatives, the β- epimer of the C_1-side-chain is more stable than the α-epimer, contrary to the limonin series [e.g. merolimonol (XII) ⟶ the acid (XXVI)].

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[12] A.D. Cross, Quart.Rev. 14, 326 (1960).

Tetrahedron Letters No. 10, pp. 333-336, 1961. Pergamon Press Ltd. Printed in Great Britain.

PERCHLOROFULVALENE

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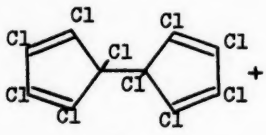
St. Louis, Missouri

(Received 15 May 1961)

DECACHLOROBI-2,4-cyclopentadien-1-yl, I, reacts with esters of trivalent phosphorus, II, according to the stoichiometry:



$$+ \text{-P(-O-R)-} \longrightarrow C_{10}Cl_8 + \text{-P(Cl)(=O)-} + RCl \quad (1)$$

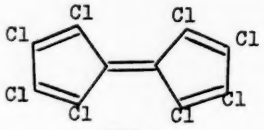
I II III

For example, the addition of ethyl phosphite to I yielded III, dark blue crystals [λ_{max} (isooctane) 386 mμ, log ε 4.55 and 590 mμ, log ε 2.71; I.R. maxima 6.55, 7.95, 8.09, 8.61, 13.00, 14.21 and 14.50μ, no C-H modes; decomposes at 200° (without melting);[1] Found: C, 29.1; H, 0.5; Cl, 69.2; mol. wt., 402 (boiling point elevation, benzene); $C_{10}Cl_8$ requires: C, 29.8; Cl, 70.2%; mol. wt., 403.8] in 55% conversion (66% yield, based on I), $(EtO)_2P(O)Cl$ (b.p. 40°/0.4 mm), 77% conversion, and ethyl chloride (identified by its infrared spectrum, gas phase).

[1] An investigation of the decomposition product, for which a dimeric structure is indicated, is being carried out.

III (0.02 mole) absorbed rapidly about 13.5 equivalent moles of hydrogen [in ethanol and in the presence of platinum oxide at 50 lb/in^2 (3.4 atm) and at 25°, complete in 15 min] to yield bicyclopentyl, IV, (b.p. 60°/7 mm, n_D^{20} 1.4632; reported: b.p. 190°, n_D^{20} 1.4640; identity confirmed also by its infrared spectrum)[2,3] in 77% yield.

These data support the octachlorobicyclopentadienylidene, (perchlorofulvalene), IIIa structure for III and indicate that the phosphorous ester acts as a simple and smooth dechlorinating agent for I.[4]



IIIa

The structure IIIa, however, had already been assigned by Riemschneider to a crystalline compound, V, m.p. 62°, obtained by the reduction of hexachlorocyclopentadiene with zinc and hydrochloric acid.[5]

Subsequently McBee, Roberts and Idol have shown that V was actually 1,2,3,4-tetrachlorocyclopentadiene, m.p. 62°, and reported that perchlorofulvalene was a yellow crystalline compound, VI, m.p. 345-347°, obtained by the thermal dechlorination of I.[6] Their assignment was supported by

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[2] S.W.Ferris, Handbook of Hydrocarbons. Academic Press, New York (1955).

[3] American Petroleum Institute Research Project 45; Spectrum No. 1088.

[4] The dechlorinating action of phosphites on hexachloroethane was reported by G.Kamai [Izv.Akad.Nauk SSSR, Otdel.Khim.Nauk 923 (1952); Bull.Acad.Sci.U.R.S.S., Classe Sci.Chim. 819 (1952)].

[5] R.Riemschneider, Chem. & Ind. 64, 698, footnote 9 (1950); R.Riemschneider, Z.Naturf. 6B, 463 (1951).

[6] E.T.McBee, J.D.Idol, Jr. and C.W.Roberts, J.Amer.Chem.Soc. 77, 4375 (1955); E.T.McBee, C.W.Roberts and J.D.Idol, Jr., Ibid. 77, 4942 (1955).

elemental analyses, mol. wt., spectral data and by hydrogenation of VI over copper chromite to IV.

In view of the conflicting results the reinvestigation of the data cited in support of the structure of VI seemed necessary.

A synthetic sample of VI,[6] m.p. 345-347°, had analyses and ultraviolet absorption spectra (Found: C, 29.24; Cl, 70.15%; Calc. for $C_{10}Cl_8$: C, 29.75; Cl, 70.25%; λ_{max} (cyclohexane) 268 mμ, log ε 4.426; 278 mμ, log 4.510) in agreement with those reported, but differed in the data of the mol. wt. determinations [Found: 564 (benzene, boiling point elevation), 548 (Rast, camphor)] from the reported figure [429 (benzene, vapor pressure depression);[6] Calc. for $C_{10}Cl_8$: 404].

VI absorbed [in a standard Parr apparatus, in ethanol and in the presence of platinum oxide, at 50 lb/in^2 (3.4 atm) and at 25°] approximately 16 equivalent moles of hydrogen in 20 hr and yielded a white crystalline product, VII [m.p. 96-97°; Found: C, 90.27; H, 9.03; Cl, 0.0%; mol. wt., 202 (Rast)]. The mol. wt. thus indicates that hydrocarbon VII has a C_{15} skeleton. Subsequently VII was found to be identical with trindan, $C_{15}H_{18}$, by m.p., mixed m.p. and infrared and ultraviolet spectra.[7] Trindan resisted hydrogenation in the presence of platinum oxide, (even in highly acidic medium) a behavior known for and expected from fully alkylated benzenes.[8]

These data indicate that VI, m.p. 345-347°, is actually $C_{15}Cl_{12}$, (mol. wt., 606) and, most likely, a tetracyclic chlorocarbon with three five membered rings and with six double bonds, such as a dodecachlorodihydro-trindene IX.[9] VI on mild hydrogenation yields trindan, $C_{15}H_{18}$, in 83% yield.

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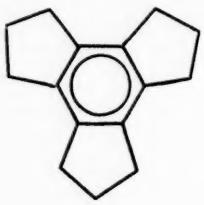
[7] O.Wallach, Ber.Dtsch.Chem.Ges. 30, 1094-1096 (1897).

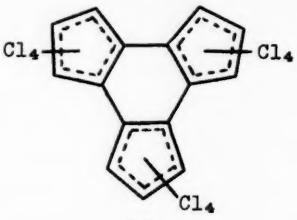
[8] See, e.g. C.M.Buess and D.Lawson, Chem.Rev. 60, 322 (1960) on various attempts to hydrogenate dodecahydrotriphenylene.

[9] Present data do not allow the definition of the position of double bonds in IX and the selection of a single structure from the numerous possibilities. Mechanistic considerations, however, suggest IXa (dodecachloro-3b,6b-dihydro-3aH-trindene) as a likely structure for VI.[10]

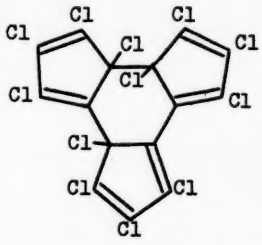
The formation of IV from VI under drastic (copper chromite) hydrogenation conditions[6] is probably due to the hydrogenolysis of the chlorocarbon.



Trindan



IX



IXa

The formation of VI takes place probably by a free radical mechanism which involves the pyrolysis of I into pentachlorocyclopentadienyl radicals; these on addition to I yield the C_{15}-unit, from which the final structure (such as IXa) is derived by elimination of two chlorine atoms, cyclization and a final elimination of a third chlorine atom. The overall stoichiometry is indicated by (2):

$$3\ C_{10}Cl_{10}(I) \longrightarrow 2\ C_{15}Cl_{12}(VI) + 3\ Cl_2 \qquad (2)$$

Acknowledgement is expressed to Dr. B.Katlafsky for the spectra, to Mr. John O'Sullivan for the elemental analyses and to Dr. A.J.Speziale for helpful suggestions and his interest in the program.

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[10] The crystal and molecular structure of VI is being investigated by Dr. P.J.Wheatley at Monsanto-Zurich Research Laboratories.

Tetrahedron Letters No. 10, pp. 337-340, 1961. Pergamon Press Ltd. Printed in Great Britain.

KINETICS OF THE ACID-CATALYZED INTERCONVERSION OF 3-HYDROXYCYCLOHEXANONE AND 2-CYCLOHEXENONE: REINTERPRETATION OF THE DECOMPOSITION OF 3-ALKOXYALLYLIC ALCOHOLS

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(Received 20 May 1961)

A VERY useful synthesis of α,β-unsaturated aldehydes and ketones involves reduction of the enol ether of a β-dicarbonyl compound and treatment of the resulting hydroxy enol ether with aqueous acid (equation 1).[1-11] In the course of studying the mechanisms of several reactions which center about

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[1] R.L. Frank and H.K. Hall, Jr., J.Amer.Chem.Soc. 72, 1645 (1950).

[2] P. Siefert and H. Schinz, Helv.Chim.Acta 34, 728 (1951).

[3] J.P. Blanchard and H.L. Goering, J.Amer.Chem.Soc. 73, 5863 (1951).

[4] R.B. Woodward, F. Sondheimer, D. Taub, K. Heusler and W.M. McLamore, J.Amer.Chem.Soc. 74, 4225 (1952).

[5] H. Conroy, J.Amer.Chem.Soc. 74, 3046 (1952).

[6] E.A. Braude and O.H. Wheeler, J.Chem.Soc. 320 (1955).

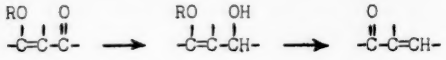
[7] O.P. Vig, T.P. Sharma and S.M. Mukherji, Chem. & Ind. 381 (1956).

[8] R.D. Campbell and H.M. Gilow, J.Amer.Chem.Soc. 82, 2389 (1960).

[9] R.F. Church, R.E. Ireland and J.A. Marshall, Tetrahedron Letters No. 1, 34 (1961); the authors are grateful to Professor Ireland for communicating his results to us prior to publication and for many stimulating discussions of this problem.

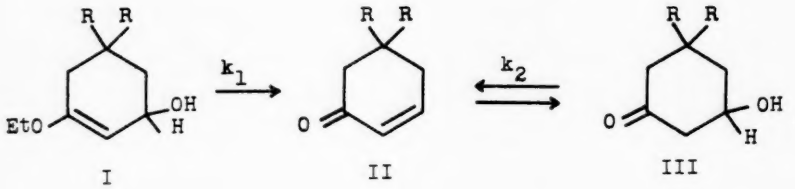
[10] G.F. Woods, P.H. Griswold, Jr., B.H. Armbrecht, D.I. Blumenthal and R. Plapinger, J.Amer.Chem.Soc. 71, 2028 (1949), employing Grignard reagents in the first step, used the scheme to prepare unsaturated ketones with another substituent at C_β.

[11] J.F. Arens and D.A. Van Dorp, Rec.Trav.Chim. 67, 973 (1948) prepared the intermediates by a different method.



(1)

β-hydroxy ketones, we have obtained kinetic information which clarifies the mechanism of reaction (1) and contradicts most previous interpretations.[2-5,8,10]



I II III

Treatment of 3-ethoxy-2-cyclohexenone[12] with lithium aluminum hydride furnished the alcohol (I, R=H), b.p. 69°/0.7 mm, n_D^{25} 1 4843 (Found: C, 67.33; H, 9.84) which was stable toward alkali and in the absence of moisture. The compound was converted quantitatively to cyclohexenone (II, R=H) by 10^{-3} M hydrochloric acid at 0° or by solution in water at room temperature; in neither case could any hydroxy ketone (III) be found. The alcohol (I, R=CH_3) b.p. 99.0-100.5°/5 mm (Found: C, 70.68; H, 10.60) prepared by reduction of 5,5-dimethyl-3-ethoxy-2-cyclohexenone[1] was equally sensitive to "hydrolysis". The rate of formation of cyclohexenone from I (R=H) was followed spectrometrically at 25.2° C in both phosphate and ammonia buffers between pH 7 and 9. The reaction is clearly acid-catalyzed, with first-order rate constants k_1 (min^{-1}) described by the equation: $\log k_1 = -0.945\ pH + 5.52$.

Reaction of dihydroresorcinol with β-mercaptoethanol and p-toluenesulfonic acid in benzene furnished both the mono-hemithioketal, b.p. 90°/0.05 mm (Found: C, 55.61; H, 7.0), and the bis-hemithioketal, m.p. 61°

[12] E.G. Meek, J.H. Turnbull and W. Wilson, J.Chem.Soc. 811 (1953).

(Found: C, 51.72; H, 7.09). Reduction of the former with lithium aluminum hydride yielded the corresponding alcohol, b.p. 110-111°/0.5 mm (Found: C, 54.96; H, 8.11; S, 18.36) which was converted by refluxing in acetone with Raney nickel to 3-hydroxycyclohexanone (III, R=H) b.p. 75.0-75.5°/0.25 mm, n_D^{25} 1.4831 (Found: C, 63.17; H, 8.89). The hydroxy ketone was not measurably affected by 10^{-3} M hydrochloric acid. In 0.10-5.0 M hydrochloric acid, either the hydroxy ketone (III) or cyclohexenone (II) is converted to an equilibrium mixture in which (II)/(III) = 2.36 $\pm$ 0.09 (average of 10 experiments).

Measurement of the rate of dehydration of III in 0.10-5.0 M hydrochloric acid gave values for the first-order rate constant k_2 which were accurately proportional to neither acid concentration nor the Hammett acidity

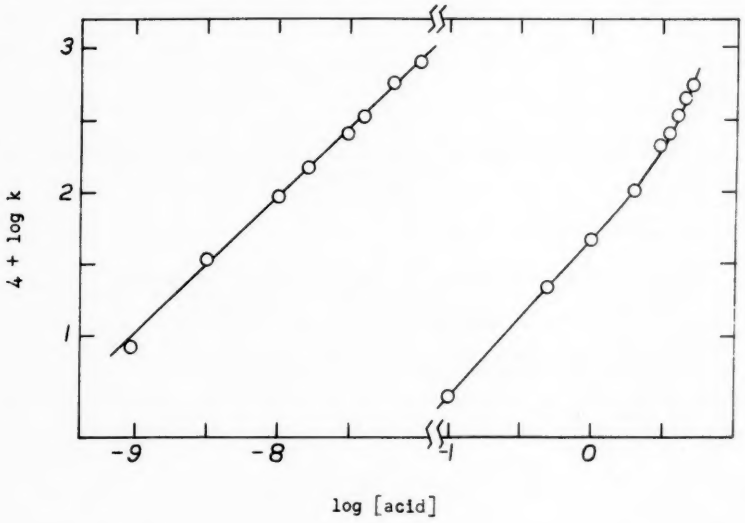
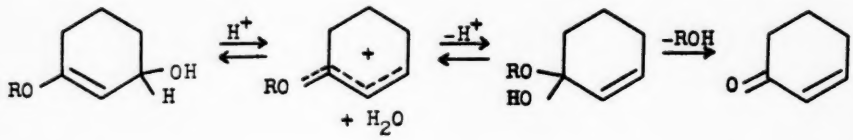


FIG. 1.

First-order rate constants (min^{-1}) for the formation of cyclohexenone from 3-ethoxy-2-cyclohexen-1-ol (left) and from 3-hydroxycyclohexanone (right) at 25.2°.

function h_o, although both conditions were approximated at the lower acidities.[13] Comparison of the rates of formation of cyclohexenone from I and from III (Fig. 1) shows that the hydroxy ketone dehydrates too slowly by a factor of ca. 10^8 to be an intermediate, as has been assumed,[2-5,8,10] in the "hydrolysis" of the hydroxy enol ethers. Thus some especially favored path from I to II takes precedence over the normal hydrolysis of the enol ether function. Consideration of the kinetic information and the well-known rearrangement of allylic alcohols[14] leads us to suggest the mechanism of equation (2). A more detailed discussion will follow.



(2)

We are indebted to Gwyn V. Hudson for some exploratory experiments, and to the National Institutes of Health for partial support (RG 5780).

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[13] Similar kinetic behavior in the acid-catalyzed dehydration of certain acyclic β-hydroxy ketones has been reported: D.S. Noyce and W.L. Reed, J.Amer.Chem.Soc. 80, 5539 (1958).

[14] E.A. Braude, Quart.Rev. 4, 407 (1950) clearly anticipated this mechanism for the reaction under discussion.

Tetrahedron Letters No. 10, pp. 341-346, 1961. Pergamon Press Ltd. Printed in Great Britain.

RACEMIZATION AND RADIO-CHLORIDE EXCHANGE OF p-CHLOROBENZHYDRYL CHLORIDE IN ACETONE[1a]

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(Received 29 May 1961)

IT has been previously reported[2] from these Laboratories that first order racemization rate constants (k_a) of p-chlorobenzhydryl chloride are substantially greater than radio-chloride exchange (k_e) or solvolysis (k_t) rate constants in acetic acid[2a] (D = 6), acetone[2b] (D = 21), and even 80% aqueous acetone[2c] (D = 30). In all three solvents it is necessary to distinguish between ionization and dissociation and to consider explicitly the role of intermediate ion pairs.

In dry acetone, the poorest ionizing[3] of the above-mentioned solvents, we have found our former polarimetric rate constants[2b] to be in error, these being unaccountably high. It is thus necessary to revise our account of the competition between ionization and chloride displacement processes in this solvent. The new data show that either chloride displacement or ionization may be made dominant under suitable conditions in acetone. Ion pair return with racemization, but without radio-chloride exchange, which

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[1a] Research supported by the National Science Foundation; [b] On leave of absence from the Dept. of Inorganic and Physical Chemistry, University of Liverpool.

[2a] S. Winstein, J.S. Gall, M. Hojo and S. Smith, J.Amer.Chem.Soc. 82, 1010 (1960); [b] S. Winstein and J.S. Gall, Tetrahedron Letters No. 2, 31 (1960); [c] S. Winstein, M. Hojo and S. Smith, Ibid. No. 22, 12 (1960).

[3] S.G. Smith, A. Fainberg and S. Winstein, J.Amer.Chem.Soc. 83, 618 (1961).

accompanies ionization of p-chlorobenzhydryl chloride, is even more important than was formerly indicated.

In Table 1 are listed representative first order polarimetric and radio-chloride exchange rate constants for p-chlorobenzhydryl chloride in acetone at 75°. The anhydrous acetone solvent, b.p. 56.2°, was reagent grade material treated with Linde Molecular Sieve Type 4A and fractionated.[3] Radio-labeled tetrabutylammonium and lithium chlorides were employed for both polarimetric and exchange kinetic runs. Optically active p-chlorobenzhydryl chloride,[2c] analytically pure, from treatment of active alcohol with hydrogen chloride in pentane at -80°C, was most often used for both racemization and exchange measurements.

In several runs without added salts, active p-chlorobenzhydryl chloride was observed to racemize with satisfactory first order kinetics, the average k_a being[4] $(1.38 \pm 0.05) \times 10^{-6}$ sec^{-1} (Table 1). Racemization rate was increased only slightly by added tetrabutylammonium perchlorate (Bu_4NClO_4), but very greatly by added tetrabutylammonium chloride (Bu_4NCl). At the higher Bu_4NCl concentrations, the (k_a/k_e) ratio is not far from 2, the value first observed by Hughes and his coworkers[5] for several halides whose exchange in acetone occurs with Walden inversion. The (k_a/k_e) ratios and the kinetic form of the racemization and exchange reactions in the presence of substantial concentrations of Bu_4NCl are consistent with predominant attack by chloride ion on covalent RCl or on an intimate ion pair with retained configuration. Treating the exchange reaction as though

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[4] This racemization rate constant is approximately an order of magnitude smaller than the value previously reported.[2b] The former measurements were made with active chloride prepared from the alcohol with thionyl chloride in benzene. The exact cause of the previous high k_a values is not clear.

[5] E.D. Hughes, F. Juliusburger, S. Masterman, B. Topley and J. Weiss, J.Chem.Soc. 1525 (1935); 1173 (1936).

Table 1

Summary of Racemization and Radio-Chloride Exchange Rates in Acetone at 75.0°

[RCl] 10^2 M	[Salt] 10^3 M	k Values (sec^{-1}) $10^6 k_a$	$10^6 k_e$	(k_a/k_e)
9.32		1.34		
9.34		1.34		
9.34		1.45		
13.51	17.36[a]	1.95		
Bu_4NCl*				
7.65	8.51	34.4	16.16	2.1
7.34	8.51	34.0	16.0	2.1
14.26	5.10	23.5	10.03	2.3
10.56	0.851	4.70		
5.64	0.851		2.14	2.2
6.38	0.166		0.42	(4.8)
LiCl*				
9.15	11.59	3.46	0.830	4.2
7.78	5.80	2.70	0.473	5.7
5.68	1.39	1.82		
8.84	1.39		0.233	7.8
7.38	0.474		0.135	(11)
6.64	0.190	1.50		
9.86	0.190		0.702	21
9.47	0.095		0.053	25

[a] Bu_4NClO_4

it is due entirely to attack by dissociated chloride ion,[6] a satisfactory bimolecular exchange rate constant, k_{2e}, equal to ca. 3×10^{-3} l. mole^{-1} sec^{-1}, is given by the data. At the lowest Bu_4NCl concentration investigated, the (k_a/k_e) ratio is substantially higher than 2, namely 4.8.

Addition of the much less dissociated lithium chloride instead of the tetrabutylammonium salt gives much smaller accelerations of racemization rate. Also, even at the highest LiCl concentrations, the (k_a/k_e) ratios are well above 2, being 4-6 at 0.01-0.005 M salt. As salt concentration is lowered, (k_a/k_e) rises, the value being 25 at ca. 1×10^{-4} M. Estimating chloride ion concentrations from the known dissociation constant for lithium chloride,[6] calculated exchange rates due to the chloride ion displacement process may be obtained with the aid of the k_{2e} value of 3×10^{-3} l. mole^{-1} sec^{-1}. These calculated displacement rates approximate the observed exchange rates even at the lowest salt concentration. Therefore, even at 10^{-4} M salt, most of the exchange reaction may be ascribed to chloride ion displacement. On this basis, the (k_a/k_e) ratio would be much larger than 25, probably at least 10^2, if chloride displacement were not contributing.

The general available evidence suggests that the racemization without exchange involves ionization. For example, the racemization rates display an appropriate solvent sensitivity,[3] the solvent sequence of k_a values at 25° being: 80% acetone, ca. $2 \times 10^4 \simeq$ AcOH, ca. $2 \times 10^4 >$ Me_2CO, 1. Thus, ion pairs from ionization of p-chlorobenzhydryl chloride in acetone lose configuration and return to racemic chloride much more often than they dissociate or exchange their anion partner with external chloride ion.

There is a variety of very recent evidence for benzhydryl derivatives in both hydroxylic and non-hydroxylic solvents demonstrating that racemiza-

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[6] S. Winstein, L.G. Savedoff, S. Smith, I.D.R. Stevens and J.S. Gall, Tetrahedron Letters No. 9, 24 (1960).

tions and isomerizations by way of ion pairs can be much more rapid than accompanying exchanges or solvolyses. Thus, for p-chlorobenzhydryl chloride, (k_a/k_t) is ca. 30 in acetic acid[2a,7] and ca. 3 in 80% acetone.[2c] For $C_6H_5CHClC_6D_5$ and $C_6H_5CDClC_6D_5$, Pocker[8] has recently found that (k_a/k_t) is ca. 3 in 80% acetone, while (k_a/k_e) is ca. 20 and 100 in $MeNO_2$ and liquid SO_2, respectively. He has also ascribed his results to ion pairs which lose their configuration and return to racemic chloride rather than dissociate, solvolyze or exchange anion partners. Isomerization of benzhydryl thiocyanates to isothiocyanates has been reported by Iliceto[9] to occur in acetonitrile more rapidly than exchange with labeled thiocyanate ion. Also, isomerization of benzhydryl thionbenzoates to thiolbenzoates has been observed by Dr. S. Smith[10] to proceed much more rapidly than solvolysis in solvolyzing solvents. Further, O^{18}-labeled benzhydryl p-nitrobenzoate has been found by Professor H. Goering[11] to undergo oxygen scrambling more rapidly than solvolysis in aqueous acetone. The rates of the various racemizations and isomerizations being measured by the different investigators all represent characteristic, but not identical, fractions of the rates of ionization of the various substrates under the prevailing conditions.

It is interesting to contrast the high (k_a/k_e) ratio for p-chlorobenzhydryl chloride in the presence of low LiCl concentrations with the value observed with low concentrations of $HgCl_2$ in acetone.[7] In the presence of this electrophilic catalyst, k_a and k_e are both increased

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[7] A. Ledwith and M. Hojo, unpublished work.

[8] Y. Pocker, Proc.Chem.Soc. 140 (1961).

[9a] A. Iliceto, A. Fava and U. Mazzucato, Tetrahedron Letters No. 11, 27 (1960); [b] A. Iliceto, A. Fava, O. Rossetto and U. Mazzucato, J.Amer. Chem.Soc. in press; [c] A. Iliceto, private communication.

[10] S.G. Smith, private communication.

[11] H. Goering, private communication.

enormously and are linear in $HgCl_2$ concentration. At all salt concentrations investigated at 25°, the (k_a/k_e) ratio is (1.50 ± 0.03). This exact 3:2 ratio of racemization to exchange is in line with an ionization of RCl to $R^{\oplus}HgCl_3^{\ominus}$ and regeneration of RCl from an $R^{\oplus}HgCl_3^{\ominus}$ pair which has become racemic and has three equivalent chlorine atoms, but is still so constituted that two chlorine atoms are from the original labeled $HgCl_2$ and one is from the RCl. Thus, the $HgCl_3^{\ominus}$ group which donates chloride ion to regenerate covalent RCl has not exchanged chloride with other labeled $HgCl_2$ molecules.

Tetrahedron Letters No. 11, pp. 347-352, 1961. Pergamon Press Ltd. Printed in Great Britain.

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CHEMISTRY OF DIIMIDE. SOME NEW SYSTEMS FOR THE HYDROGENATION OF MULTIPLE BONDS

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(Received 26 May 1961)

THE fact that hydrazine can serve as a reagent for the hydrogenation of carbon-carbon unsaturation appears to have been realized first by Hanus and Vorisek[1] over thirty years ago after a reinvestigation of still earlier observations on the formation of stearyl hydrazide from the interaction of glyceryl oleate with hydrazine.[2] Their work established that oleic acid could be hydrogenated to stearic acid by (1) treatment with hydrazine[1] and (2) reaction with hydrazine and sulfur.[3] This accidental but truly novel discovery produced hardly a stir in the rapid stream of chemical events of the subsequent period and apparently chance alone determined the encounter of related reductive processes in other laboratories. In 1941 Fischer reported that vinyl groups in chlorins and porphyrins are selectively reduced to ethyl groups by hydrazine under mild conditions,[4] a finding confirmed more recently by Woodward and co-workers at Harvard.[5] Lately,

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[1] J. Hanus and J. Vorisek, Coll.Czech.Chem.Comm. 1, 223 (1929).

[2] J. Hanus, Chem.Listy 29, 24 (1905).

[3] J. Vorisek, Chem.Listy 26, 286 (1932).

[4] H. Fischer and H. Gibian, Liebigs Ann. 548, 183 (1941); Ibid. 550, 208 (1942).

[5] R.B. Woodward and co-workers, personal communication.

the reaction of gibberellic acid with hydrazine was found to yield tetrahydrogibberellic acid,[6] and in our own laboratory it was noticed that certain conjugated dienes in the triterpene series suffer hydrogenation under Wolff-Kishner reduction conditions.[7] Still more recent preliminary reports[8] disclose that a variety of acyclic olefins are reduced by treatment with hydrazine and also that the presence of oxygen is necessary for the reduction. These prompt us to report work which we have carried out on the nature and mechanism of this unique hydrogenation.

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In our view it seemed rather unlikely that hydrazine itself was the principal hydrogenating species, regardless of which reaction path might be considered (including modes for addition of hydrogens singly or pair-wise to C=C), and relatively probable that a reactive intermediate occurring between hydrazine and the final product of its oxidation, molecular nitrogen, serves as the true reductant; more specifically the hitherto elusive and very unstable substance diimide (HN=NH) appeared to be an outstanding candidate for this function. The energetics of hydrogen addition - elimination are pertinent:

$$H_2H\text{-}NH_2 \rightarrow HN{=}NH + H_2 \qquad \Delta\underline{H} \sim +26.5 \text{ kcal/mole}$$

$$HN{=}NH \rightarrow N_2 + H_2 \qquad \Delta\underline{H} \sim -48.7 \text{ kcal/mole}$$

$$H_2 + C{=}C \rightarrow CH\text{-}CH \qquad \Delta\underline{H} \sim -28 \pm 5 \text{ kcal/mole}$$

Whereas the direct transfer of hydrogen from hydrazine to an olefin is at most only slightly exothermic (and probably very slow), the corresponding change from diimide is highly favored energetically ($\sim$ 70 kcal/mole),[9]

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[6] B.E. Cross, J.Chem.Soc. 3022 (1960).

[7] E.J. Corey and J. Klein, unpublished observations.

[8] F. Aylward and M. Sawistowska, Chem. & Ind. 404, 433 (1961).

[9] S.N. Foner and R.L. Hudson, J.Chem.Phys. 28, 719 (1958); for an infrared study see E.J. Blau, B.F. Hochheimer and H.J. Unger, J.Chem. Phys. 34, 1060 (1961).

and ought to require only moderate activation energy.

The detection of diimide, which was first attempted unsuccessfully by Thiele[10] using a classical preparative approach, has been accomplished only recently by mass spectrometry[9] of the gaseous products from electrodeless electrical discharge through a stream of hydrazine or hydrazoic acid vapor. And, indeed, evidence derives from this work[9] that diimide persists in the solid state at -195°C! Diimide, then, is a substance of appreciable lifetime; its decomposition to molecular hydrogen and nitrogen is not inevitable.

The notion that diimide is the reactive hydrogenator in hydrazine-olefin systems is strongly supported by our experimental studies. We find that hydrazine per se is inoperative as a reducing agent, but that the combination with various oxidizing agents is effective; moreover, these oxidizing agents are generally those which have been found to convert hydrazine to nitrogen by a reaction path which appears to involve diimide.[11,12] In our experience the most convenient systems for reduction of unsaturated compounds with hydrazine are hydrazine-oxygen (air)-copper ion (trace) (O system) and hydrazine-hydrogen peroxide- copper ion (trace) (P system). Copper ion, a powerful catalyst for the oxidation of hydrazine,[11] enormously accelerates the hydrogenation of multiple bonds in both O and P systems. The reduction of the azobenzene to hydrazobenzene in methanol takes place completely (isolated yield 95%) with either the O or P system and is especially useful as a rapid test because its progress can be followed visually; the following observations have been made in this case (methanol

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10 J. Thiele, Liebigs Ann. 271, 127 (1892).

11 L.F. Audrieth and B.F. Ogg, The Chemistry of Hydrazine Chapter 6. John Wiley, New York (1951).

12 W.C.E. Higginson in Recent Aspects of the Inorganic Chemistry of Nitrogen, p. 95. Special Publication No. 10 of the Chemical Society, London (1957).

solution at 25°) and serve to exemplify the general behavior noted above.

(1) Little or no reaction takes place in the absence of an oxidizing agent over prolonged periods.

(2) The reduction is very slow in the presence of oxygen or of hydrogen peroxide if heavy metal ions (especially copper) are rigorously excluded ($t_{1/2}$ several days) but becomes very fast upon addition of cupric ion; in the presence of excess hydrazine and hydrogen peroxide the reaction becomes almost instantaneous at or above ca. 0.001 N copper ion.

(3) In the P system with excess hydrazine more than an equimolar amount of hydrogen peroxide is required to reduce all of the azobenzene (usually about three equivalents). Clearly, the reactive intermediate is being diverted by some competing process, probably self-destruction and/or hydrogenolysis of hydrazine or hydrogen peroxide.

The coincidence of those factors which accelerate the oxidation of hydrazine to nitrogen via diimide[11,12] and those which accelerate reduction is apparent from the above data. Further evidence supporting the key role of diimide in these systems have been obtained from the study of the reducing properties of potassium azodiformate (KOOCN=NCOOK). This substance undergoes rapid and quantitative decomposition in water according to the equation.[10,13]

$$2KOOCN=NCOOK + 4H_2O \longrightarrow H_2N\text{-}NH_2 + 4KHCO_3 + N_2$$

The reaction is first-order in azodiformate and also general acid catalyzed;[13]

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[13] C.V. King, J.Amer.Chem.Soc. 62, 379 (1940).

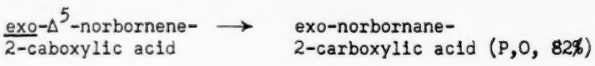
the intermediacy of diimide seems inescapable with its ultimate fate being sealed by a capacity to function both as a hydrogen acceptor and as a powerful hydrogen donor;

$$2HN{=}NH \longrightarrow H_2N\text{-}NH_2 + N_2 \qquad \Delta H \sim -75 \text{ kcal/mole}$$

The addition of excess potassium azodiformate to azobenzene in aqueous methanol results in rapid reduction to produce hydrazobenzene. An excess of the potassium salt is required for complete reduction doubtless because of self-annihilation of diimide. Olefins can also be reduced by this reagent but the process is not practical preparatively because a large excess of the reductant is required.

The reduction of a considerable number of olefins has been carried out using the P, the O and the azodiformate systems. In general acetylenic bonds and mono- or di-substituted double bonds are reduced with ease and tri-substituted bonds more difficultly. The following illustrations are provided; yields given are those for purified products and may not be optimal although an excess of reductant was generally employed.

maleic acid	⟶	succinic acid (O, 82%)
fumaric acid	⟶	succinic acid (P, 76%)
diphenylacetylene	⟶	1,2-diphenylethane (O, 80%)
trans-stilbene	⟶	1,2-diphenylethane (O, 88%)
gibberellic acid	⟶	tetrahydrogibberellic acid (P, 74%)
butyne-1,4-diol	⟶	butane-1,4-diol (P, 40%) (as succinic acid)
cholesterol	⟶	cholestanol (O, 20%)
cis-Δ^4-cyclohexene-1,2-dicarboxylic acid	⟶	cis-cyclohexane-1,2-dicarboxylic acid (P, 78%)



Efforts to trap diimide by Diels-Alder interception so far have been inconclusive; thus, reaction of cyclopentadiene with the P system produced cyclopentene and cyclopentane, but only minor amounts of a basic liquid mixture.

A subsequent paper[14] will report on the stereochemistry of reductions by diimide. Work in progress includes the study of reactions of externally generated diimide as well as the more general application of this interesting substance in organic chemistry. The question of the stereochemistry of diimide itself also demands attention.

This work is reported simultaneously with that from the laboratory of Prof. S. Hünig through mutual agreement.

Acknowledgements - We thank the National Science Foundation for fellowships to W.L.M. (predoctoral) and D.J.P. (postdoctoral) and the Higgins Fund of Harvard University for generous financial support.

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[14] E.J. Corey, D.J. Pasto and W.L. Mock, J.Amer.Chem.Soc. In press.

Tetrahedron Letters No. 11, pp. 353-357, 1961. Pergamon Press Ltd. Printed in Great Britain.

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REDUKTIONEN MIT DIIMID

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(Received 19 May 1961)

BEI der Wolff-Kishner Reduktion von langkettigen, ω-ungesättigten Ketocarbonsäuren beobachteten Hünig und Eckardt,[1] dass die olefinische Bindung teilweise reduziert wird.

Diese Nebenreaktion tritt schon bei der Hydrazonbildung ein und kann durch Ausschluss des Luftsauerstoffs völlig unterdrückt werden.[1] Damit war gezeigt worden, dass die merkwürdige, in Abwesenheit von Katalysatoren verlaufende Hydrierung einer isolierten olefinischen Doppelbindung mit Hydrazin, die in der Literatur schon mehrfach erwähnt ist,[2-10] nicht diesem selbst, sondern einem Dehydrierungsprodukt des Hydrazins zukommen muss.[11]

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[1] S. Hünig u. G.W. Eckardt, Diplomarbeit Marburg (1959); Diss. Marburg (1960).

[2] P. Falciola u. A. Mannino, Ann.Chim.Appl. 2, 351 (1914).

[3] P. Falciola, Gazz.Chim.Ital. 50, I, 162 (1920).

[4] J. van Alphen, Rec.Trav.Chim. 44, 1064 (1925).

[5] J. Hanus u. J. Vorisek, Coll.Trav.Chim.Tchecosl. 1, 223 (1929).

[6] J. Vorisek, Chem.Listy 26, 285 (1932).

[7] J. Vorisek, Coll.Trav.Chim.Tchecosl. 5, 466 (1933).

[8] M.K. Pajari, Fette u. Seifen 51, 347 (1944).

[9] E.L. Callery, Brit.Pat. 621, 037 (1945).

[10] F. Aylward u. C.V. Narayano Rao [a] J.Appl.Chem. 6, 248 (1956); [b] Ibid. 6, 559 (1956); [c] Ibid. 7, 134 (1957); [d] Ibid. 7, 137 (1957).

[11] Die Hydrierung von konjugierten Doppelbindungen mit Natriumhydrazid unter Sauerstoffausschluss erfolgt vermutlich auf einem anderen Wege. Th. Kaufmann, H. Hacker, Ch. Kosel u. W. Schoeneck, Angew.Chem. 72, 918 (1960).

Auf die Bedeutung des Luftsauerstoffs ist bereits hingewiesen worden.[10a]

Der neuerliche Einsatz dieser Reaktion für präparative Zwecke[12] sowie deren Studium in einem anderen Arbeitskreis[13] veranlassen uns, unsere bisherigen Ergebnisse auf diesem Gebiete bekanntzugeben.

Die Hydrierung von Δ^{10}-Undecensäure (als Testsubstanz) in alkalisch-wässeriger Hydrazinlösung wird ausser durch Luftsauerstoff auch durch Kalium-hexacyanoferrat-III und durch Quecksilberoxyd bewirkt. Als praktisch unwirksam unter diesen Bedingungen erwiesen sich Jod, Kaliumpermanganat und der Kupfer-II-tartratkomplex.

Die hydrierende Wirkung des Paares Kalium-hexacyanoferrat-III/Hydrazin lässt sich besonders gut studieren, da die Stöchiometrie der Hydrazinoxydation nach (a),[14,15] die der Hydrierung jedoch nach (b) zu formulieren ist.

(a) $$4[Fe(CN)_6]^{3\ominus} + H_2N\text{-}NH_2 \longrightarrow N_2 + 4H^{\oplus} + 4[Fe(CN)_6]^{4\ominus}$$

(b) $$2[Fe(CN)_6]^{3\ominus} + H_2N\text{-}NH_2 + \diagup C = C \diagdown \longrightarrow N_2 + 2H^{\oplus} + 2[Fe(CN)_6]^{4\ominus} + \underset{H}{C} - \underset{H}{C}$$

Tatsächlich stimmt der aus dem Verhältnis (verbrauchte Oxydationsaquivalente) / (entstandene Mole N_2) bestimmte Hydrierungsgrad mit dem bromometrisch ermittelten überein. Unter standardisierten (aber nicht

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12 E. Cross, J.Chem.Soc. 3028 (1960).

13 Bei einer Diskussion mit Herrn Prof. Dr. E.J. Corey in der Harvard University, Cambridge, Mass., U.S.A., am 18. April 1961, stellte sich heraus, dass das gleiche Problem dort ebenfalls bearbeitet wird. Es wurde vereinbart, die bisherigen Ergebnisse beider Arbeitskreise gleichzeitig zu veröffentlichen. S. Hünig.

14 E.J. Cuy U. W.C. Bray, J.Amer.Chem.Soc. 46, 1786 (1924).

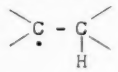
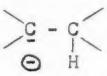
15 P.R. Ray u. H.K. Sen, Z.Anorg.Chem. 76, 380 (1912).

optimalen) Bedingungen wurden bei einem Verhältnis von $K_3[Fe(CN)_6]$: H_2NNH_2 : Olefin = 2:6:1 die in Klammern gesetzten Hydrierungsgrade erzielt.

Fumarsäure	(80)	Δ^{10}-Undecensäure	(69)
Maleinsäure	(41)	trans-Zimtsäure	(41).

Mit überschüssigem Oxydationsmittel lässt sich leicht quantitative Hydrierung erreichen.

Dass es sich bei dem hydrierenden Agens höchst wahrscheinlich um das lang gesuchte Diimid [16-18] handelt, geht aus folgenden Ergebnissen hervor:

(1) Wird Phenylpropiolsäure unter den obigen Bedingungen zu etwa 40% hydriert, so besteht die entstehende Zimtsäure offenbar nur aus der cis-Form; trans-Zimtsäure lässt sich im I.R.-Spektrum nicht auffinden. Ihr Anteil muss darnach unter 6% liegen. Die damit nachgewiesene cis-Addition des Wasserstoffs schliesst die Reaktion über Stufen wie  oder  aus.

(2) Die Hydrierung der Δ^{10}-Undecensäure in heisser alkalischer Lösung erfolgt quantitativ beim Eintragen von überschüssigem Benzolsulfhydrazid, das unter diesen Bedingungen primär nach (c) zerfallen sollte.[17]

(c) $C_6H_5SO_2NHNH_2 + OH^{\ominus} \longrightarrow C_6H_5SO_2^{\ominus} + H_2O + N_2H_2$

(d) $N_2H_2 \longrightarrow N_2 + H_2$

(e) $4C_6H_5SO_2NHNH_2 \longrightarrow C_6H_5SO_2\text{-}SC_6H_5 + C_6H_5S\text{-}SC_6H_5 + 4N_2 + 6H_2O$

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[16] J. Thiele, Liebigs Ann. 271, 127 (1892).

[17] F. Raschig, Z.Angew.Chem. 23, 972 (1910).

[18] S.N. Foner u. R.L. Hudson, J.Chem.Phys. 28, 719 (1958).

Im gleichen Sinne werden Dicyclopenten und -pentadien in siedendem, stark alkalischem Glykolmonomethyläther durch zerfallendes Benzolsulfhydrazid hydriert. Ohne Olefin schliesst sich Reaktion (d) an, da ein äquimolares Gemisch von Stickstoff und Wasserstoff entsteht, was Raschig[17] ohne experimentelle Angaben bereits beschrieben hat. Mit sinkender Alkalikonzentration geht der Wasserstoffanteil im entstandenen Gasgemisch zurück, um schliesslich die Stöchiometrie (e) der rein thermischen Zersetzung[19] zu erreichen.

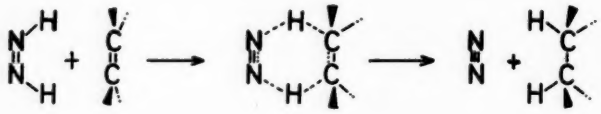
(3) Azodicarbonsaures Kalium, dessen Zerfall in wässeriger Lösung nach (f) erfolgt,[16,17,20] vermag ebenfalls

(f) $2\ ^{\ominus}OOC\text{-}N{=}N\text{-}COO^{\ominus} + 4H^{\oplus} \longrightarrow N_2 + H_2N\text{-}NH_2 + 4CO_2$

(g) $^{\ominus}OOC\text{-}N{=}N\text{-}COO^{\ominus} + 2H^{\oplus} \longrightarrow N_2H_2 + 2CO_2$

Δ^{10}-Undecensäure zu hydrieren. Das nach (g) zu erwartende Diimid[16,17] greift dabei teilweise an Stelle des zweiten Moles Azodicarbonsäure die olefinische Doppelbindung hydrierend an.

Alle vorgetragenen Ergebnisse weisen auf die intermediäre Existenz des Diimids hin. Dessen hydrierende Wirkung lässt sich vorläufig am besten als Mehrzentrenreaktion des cis-Diimids mit dem Olefin beschreiben.



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[19] D.B.P. 821 423 (1949); Farbenfabriken Bayer A.G. A.P. 2 552 065 (1951); U.S. Rubber Co. A.PP. 2 626 280, 2 673 220 (1952) U.S. Rubber Co.

[20] C.V. King, J.Amer.Chem.Soc. 62, 379 (1940).

Die Untersuchungen werden in verschiedenen Richtungen fortgesetzt.

Wir danken dem Fonds der Chemischen Industrie sowie der BASF Badischen Anilin- & Soda-Fabrik A.G., Ludwigshafen am Rhein, für die grosszügige Förderung dieser Studien.

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HYDROXYTOTAROL

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Ames, Iowa, U.S.A.

(Received 1 June 1961)

A HYDROXY totarol has been reported to be a minor constituent of Podocarpus totara.[2] Through the courtesy of Dr. B.R. Thomas we received a small sample of the product of the original isolation and have been able to inspect its chemical constitution. It is a colorless crystalline $C_{20}H_{30}O_2$ compound (Found: C, 79.1; H, 10.1. Calc.: C, 79.4; H, 10.0), m.p. 230-231°, $[\alpha]_D^{26}$ + 29° (ethanol), whose ultraviolet spectrum $\lambda_{max}^{95\%EtOH}$ 279 mμ (ε 1990) is identical with that of totarol (Ia)[3,4] and whose infrared spectra in both chloroform solution and Nujol exhibit all bands (in several instances, of different intensity) revealed by the spectra of totarol (Ia) as well as peaks at 2.99(m), 9.80(s), 9.89(s) and 10.87(m)μ, characteristic of a carbinol group. Early chromic acid oxidation experiments led to an aldehyde,[5] indicative of the presence of a primary alcohol function in the natural product. The exceedingly low yields encountered in our degradation experiments and the

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[1] Public Health Service Predoctoral Research Fellow, 1960-1961.

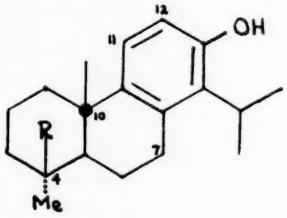
[2] C.W. Brandt and B.R. Thomas, Nature,Lond. 170, 1018 (1952).

[3] J.D.S. Goulden in W.F. Short and H. Wang, J.Chem.Soc. 2979 (1951).

[4] Dr. J.C. Dacre (University of Otago, Dunedin, New Zealand) kindly supplied us with a sample of totarol acetate.

[5] J.W. Chamberlin, unpublished observations.

availability of only a small quantity of material precluded a structure analysis by chemical means. As a consequence a proton magnetic resonance study of hydroxytotarol and various model compounds was undertaken.[6]

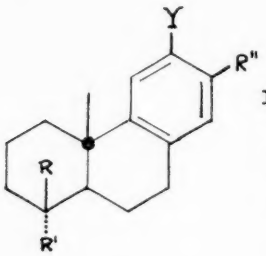


Ia, R=Me
b, R=CH_2OH

The p.m.r. spectrum of totarol (Ia) exhibits an AB quartet centered at 6.70δ (J=8.9 c.p.s.) due to the C-11 and 12 aromatic hydrogens, a low broad 4.35δ phenolic proton peak, five peaks of the expected septet for the isopropyl methine hydrogen centered at 3.07δ (J=7.2 c.p.s.), a complex multiplet at 2.78δ due to the C-7 methylene hydrogens, a doublet centered at 1.29δ (J=7.2 c.p.s.) characteristic of the isopropyl methyl groups, a 1.12δ C-10 methyl peak and two peaks, 0.94 and 0.92δ, due to the C-4 gem-dimethyl function. The spectrum of hydroxytotarol differs substantially from that of totarol (Ia) only by the replacement of the gem-dimethyl peaks by a 1.04δ methyl peak and an AB quartet centered at 3.66δ (J=10.9 c.p.s.) due to the methylene hydrogens of a hydroxymethyl group. Its isopropyl methyl groups show up as a doublet centered at 1.32δ (J=7.2 c.p.s.) and its C-10 methyl function as a 1.16δ peak. These data and the correspondence of the chemical shift of the angular methyl group in totarol (Ia) and hydroxy-

[6] Assignment of the chemical shifts of methyl groups is based on a larger study of the n.m.r. spectra of various diterpenic compounds to be published in the near future.

totarol with that of dehydroabietol (IIa),[7] 1.18δ, and O-methylpodocarpol (IIb),[8] 1.16δ, prove that hydroxytotarol possesses a C-4 hydroxymethyl function.



IIa, R=Me,R'=CH_2OH,R"=i-Pro,Y=H
b, R=CH_2OH,R'=Me,R"=H,Y=OMe
c, R=R'=Me,R"=H,Y=OMe
d, R=Me,R'=CH_2OAc,R"=i-Pro,Y=H
e, R=CH_2OAc,R'=Me,R"=H,Y=OMe

The stereochemistry of the hydroxymethyl group was resolved by the observation that an axial group shows its quartet ca. 0.4 p.p.m. downfield of that of an equatorial group. Thus, the axial systems O-methylpodocarpol (IIb) and vouacapenol (IIIa)[9,10] reveal their quartets at 3.69δ (J=11.3 c.p.s.) and 3.60δ (J=10.9 c.p.s.), respectively, while the equatorial compounds dehydroabietol (IIa) and vinhaticol (IIIb)[9,10] show four peaks centered at 3.28δ (J=10.4 c.p.s.) and 3.25δ (J=10.2 c.p.s.), respectively. On this basis hydroxytotarol possesses an axial hydroxymethyl group. Finally, the close relationship of the spectra (in position and shape of the peaks) of two sets of two similar compounds each, totarol (Ia) and hydroxytotarol vs. O-methylpodocarpane (IIc) and O-methylpodocarpol (IIb), as contrasted with the spectral differences encountered between A/B trans and cis ring

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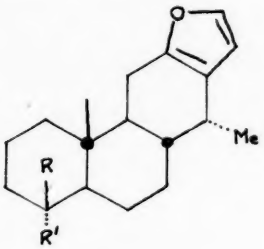
[7] L.F. Fieser and W.P. Campbell, J.Amer.Chem.Soc. 61, 2528 (1939).

[8] W.P. Campbell and D. Todd, J.Amer.Chem.Soc. 64, 928 (1942).

[9] F.E. King, D.H. Godson and T.J. King, J.Chem.Soc. 1117 (1955).

[10] Drs. F.E. King and T.J. King kindly supplied us with samples of vouacapenic and vinhaticoic acids.

systems,[6] speaks strongly in favor of a trans ring juncture in hydroxytotarol.[11] As a consequence structure Ib can be assigned to this natural product.



IIIa, R=CH_2OH, R'=Me
b, R=Me, R'=CH_2OH

It is noteworthy that the n.m.r. analysis of primary alcohols readily obtainable by the reduction of naturally occurring carboxylic acids may serve as a supplement to present methods of determination of the stereochemistry of the carboxy group in resin acids and similar substances.[12] Unfortunately it is limited to compounds possessing no other hydrogens which would yield signals in the hydroxymethyl region. Thus for example, it is hard to uncover the crucial quartet in a spectrum of iresin (IV)[13,14] from among the signals of the C-11 hydrogens and, to a less extent, those of the C-3 hydrogen. In some cases it may prove useful to inspect the spectra of the carbinol acetates in view of an appreciable downfield shift[15] of

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[11] For the stereochemistry of totarol (Ia) cf. J.A. Barltrop and N.A.J. Rogers, J.Chem.Soc. 2566 (1958) and Y.L. Chow and H. Erdtman, Acta Chem.Scand. 14, 1852 (1960).

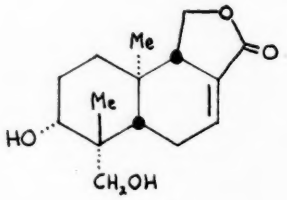
[12] Cf. E. Wenkert and B.G. Jackson, J.Amer.Chem.Soc. 80, 217 (1958).

[13] C. Djerassi and S. Burstein, Tetrahedron 7, 37 (1959).

[14] Professor C. Djerassi kindly supplied us with a sample of this compound.

[15] Cf. L.M. Jackman, Applications of Nuclear Magnetic Resonance Spectroscopy in Organic Chemistry p. 55. Pergamon Press, London (1959).

their methylene quartets, e.g.: dehydroabietyl acetate (IId)——3.84δ (J=10.5 c.p.s.); O-methylpodocarpyl acetate (IIe)——4.16δ (J=11.3 c.p.s.).[16]



IV

[16] All spectra were obtained with ca. 25% deuterochloroform solutions on a Varian Model HR60 spectrometer at 60 mc/sec with tetramethylsilane acting as internal standard. Position of the major peaks was determined by the audiofrequency side band technique, that of minor peaks by linear interpolation.

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ISOLATION AND STRUCTURE OF PERAKINE[1]

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Summit, New Jersey

Department of Chemistry, Iowa State University, Ames, Iowa

(Received 6 June 1961)

IN a reinvestigation of Rauwolfia vomitoria an apparently new alkaloid has been isolated from an aqueous-methanolic-acetic acid raffinate from the manufacture of reserpine. Carefully avoiding any contact with strong alkali, the raffinate was worked up in the following way: The bases extractable at pH 7 with methylene chloride were separated into methanol insoluble and methanol soluble nitrates. The latter were treated with ammonia, the free bases taken up into methylene chloride and the concentrated solution chromatographed on Florex. From the weakly adsorbed fraction the nitrate was prepared and this again submitted to methanolic separation. The free bases from the soluble nitrates were chromatographed on aluminum oxide. Elution with benzene containing small amounts of methanol, followed by crystallization from acetone gave crystals melting sharply at 183°. This material had similar physical properties to those reported by Kiang and Wan[2]

[1] Rauwolfia Alkaloids XL; the contents of this publication were discussed by E. Schlittler in lectures given at the University of Giessen (Germany) and at the Istituto Superiore di Sanita at Rome in March, 1961.

[2] A.K. Kiang and A.S.C. Wan, J.Chem.Soc. 1394 (1960).

for perakine, an alkaloid of unknown constitution isolated from R. perakensis.

Our alkaloid was a $C_{21}H_{22}O_3N_2$ compound, $[\alpha]_D^{26}$ + 112° ($CHCl_3$), pK'_a 5.01 (80% ethylene glycol monomethyl ether), whose analysis indicated the presence of one acetyl and one C-methyl group and the absence of O- or N-methyl functions. Its infrared spectrum (Nujol) revealed two saturated carbonyl peaks, 1739 and 1713 cm^{-1}, the first of which belonged to the acetic ester group while the latter corresponded to that of an aldehyde or ketone, as confirmed by the alkaloid's ready conversion to a monophenylhydrazone, m.p. 163° dec., infrared carbonyl band at 1740 cm^{-1}. Superimposability of the infrared spectra of the neutral product and an authentic sample of perakine[3] and the lack of m.p. depression of the two substances proved their identity.

Perakine's ultraviolet spectrum in neutral (λ_{max} 219, 257 mμ, λ_{min} 236 mμ) and in acidic medium (λ_{max} 266-267 mμ, λ_{min} 238 mμ) showed the alkaloid to be an indolenine derivative.[4] Its easy platinum catalyzed hydrogenation or chemical reduction to substances with typical indoline ultraviolet absorption tended to confirm the indolenine nature. Its most striking characteristic was the swift base-induced transformation into an indolic system. Thus addition of N KOH to an alcoholic solution of the alkaloid produced an instantaneous shift in its ultraviolet spectrum to that of an indole (λ_{max} 223, 279, 290 mμ, λ_{min} 248, 288 mμ) with the concomitant loss of its acetate group. This transformation paralleled that of N_a-demethyl-Δ^1-deoxyajmaline O-acetate[5] (I) to II. Therefore perakine appeared most

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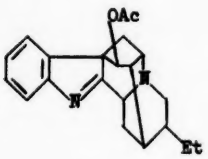
[3] The authors are grateful to Dr. Kiang for a gift of a comparison sample of his alkaloid. Whereas its specific rotation was reported as $[\alpha]_D^{23}$ -107° (EtOH) (Ref. 2) we found the rotation of Dr. Kiang's sample to be $[\alpha]_D^{24}$ + 132° ($CHCl_3$).

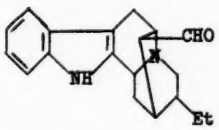
[4] In a private communication Dr. G.F. Smith, Manchester had suggested that perakine was an indolenine.

[5] M.F. Bartlett, R.F. Sklar, W.I. Taylor, E. Schlittler, R.L.S. Amai, Peter Beak, N.V. Bringi and Ernest Wenkert, in preparation.

likely to be a keto derivative of I or its epimer.



I



II

Comparison of the proton magnetic resonance spectra of perakine, compound I and the latter's 17-epimer revealed an extraordinary similarity of perakine and the acetate I in the vital regions of their spectra (see the chart below; chemical shifts are expressed in δ and spin-spin coupling constants in c.p.s.[6]). The multiplet corresponding to the aromatic protons of perakine and I was identical in the number of peaks, their height and shape. Likewise, the signals associated with the protons of C(3)-H, C(17)-H and the acetyl's methyl group were the same in chemical shift and coupling constants in the spectra of the two compounds but different from the spectrum of 17-epi-I. Whereas, however, both I and its epimer exhibited a triplet at high field characteristic of the methyl protons of their ethyl groups, perakine revealed a doublet in this region indicative of methyl protons next to a methine group. Furthermore, in contrast to the other compounds perakine showed an aldehyde proton at low field, δ 9.85, which peak, as expected,[7] shifted upfield (and was masked in the aromatic proton region) in the

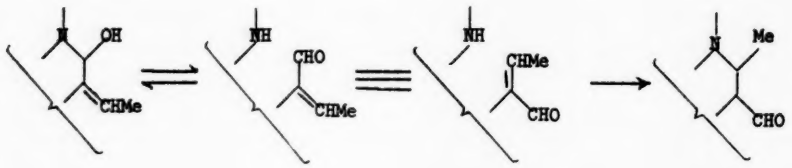
[6] The n.m.r. data were obtained on ca. 25% deuterochloroform solutions with a Varian Model HR60 spectrometer at 60 mc/sec with tetramethylsilane acting as internal standard. The position of major peaks was determined by the audiofrequency side band technique, that of minor peaks by linear interpolation.

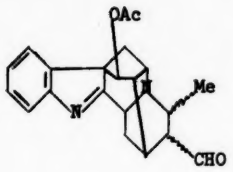
[7] Cf. D.Y. Curtin, J.A. Gourse, W.H. Richardson and K.L. Rinehart, Jr., J.Org.Chem. 24, 93 (1959).

alkaloid's phenylhydrazone. Hence perakine is a N_a-demethyl-Δ^1-deoxyajmaline O-acetate whose ethyl group has been replaced by methyl and carboxaldehyde functions.

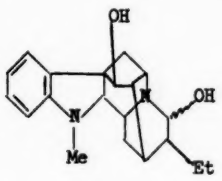
	Perakine	I	17-Epi-I
Aromatic (4 protons)	Multiplet 6.91-7.60	Multiplet 7.06-7.84	Multiplet 6.54-7.68
C(3)-H	Quartet centered at 4.21 (J=4.1, 8.4)	Quartet centered at 4.20 (J=3.4, 8.8)	Doublet centered at 4.20 (J=8.7)
C(17)-H	Doublet centered at 4.97 (J=2.1)	Doublet centered at 5.00 (J=1.8)	Doublet centered at 5.76 (J=8.7)
Me of OAc (3 protons)	2.17	2.15	2.80
C-Me (3 protons)	Doublet centered at 1.42 (J=6.3)	Triplet centered at 0.95 (J=6.0)	Triplet centered at 0.98 (J=6.0)

The above data and biosynthetic considerations permit the formulation of structure III for perakine. If it be assumed that the latter possesses the combined states of oxidation of its congeners ajmaline (IV) and sarpagine (V) at C-19, 20 and 21, the following simple chemical changes can account for its unusual aldehyde structure:

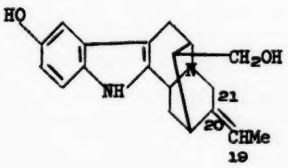




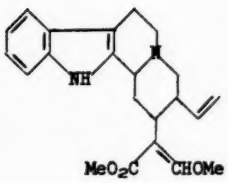
III



IV



V



VI

Perakine is the first indolenine alkaloid to be recognized from any Rauwolfia species. It constitutes the heretofore missing biosynthetic link between indole alkaloids of the corynantheine (VI) and sarpagine (V) types and indoline bases of the ajmaline (IV) variety.

Acknowledgements - We wish to express our sincere thanks to Mr. L. Dorfman's microanalytical laboratory for analytical and spectral data, to Mr. B. Korzun and his associates for paper chromatographic data, to Dr. M.J. Allen for pK'_a measurements, to Mrs. M. Kiesel for purification of a quantity of perakine and to Mr. Peter Beak for stimulating discussions on the n.m.r. spectra.

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A TRANSITION METAL-CATALYZED DIMERIZATION OF NORBORNADIENE

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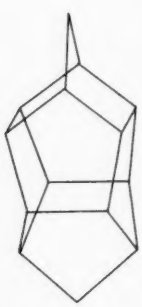
Madison 6, Wisconsin

(Received 2 June 1961)

IRRADIATION with a sunlamp of a mixture of iron pentacarbonyl and norbornadiene leads to a complex mixture of products including the tricarbonyliron complex of the diene, a number of ketones, and unsaturated dimers of the diene.[1] In addition to these we have found a saturated dimer to which we have assigned either of the novel structures I or II. It should be



I

II

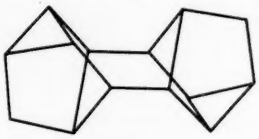
noted that several of the reaction products are formed in the absence of light,[1,2] but we have been unable to obtain the saturated dimer by heating

[1] R. Pettit, J.Amer.Chem.Soc. 81, 1266 (1959).

[2] C.W. Bird, R.C. Cookson and J. Hudec, Chem. & Ind. 20 (1960).

the reactants in the dark. Irradiation of norbornadiene alone also fails to yield this compound,[3] indicating that both light and the iron pentacarbonyl are required for the dimerization.[4]

The highly volatile saturated dimer was isolated in 2-3% yield[5] by chromatography on alumina or silica gel, on both of which it was only very weakly adsorbed. After further purification by sublimation the melting point was 165-165.5° (Found: C, 91.03%; H, 9.00%; mol. wt., 175, cryoscopic in t-butanol. Calc. for $C_{14}H_{16}$: C, 91.25%; H, 8.75%; mol. wt., 184.)[6] In the mass spectrum, the relative intensities of the peaks at 184, 185 and 186 agree within experimental error with the isotopic distribution



III

IV

[3] Since this dimerization is successful even when performed in a soft glass vessel, it is apparent that the wavelength range of the effective radiation is outside of the region in which norbornadiene absorbs appreciably. See C.F. Wilcox, Jr., S. Winstein and W.G. McMillan, J.Amer.Chem.Soc. 82, 5450 (1960).

[4] Professor R.C. Cookson has kindly informed us that this dimer is also formed by reaction of the diene with iron enneacarbonyl in the dark, so light is apparently required only for the transformation of the penta- to the enneacarbonyl. For the latter reaction, see R.K. Sheline and K.S. Pitzer, J.Amer.Chem.Soc. 72, 1107 (1950). It is of interest that irradiation of a mixture of norbornadiene with its iron tricarbonyl complex does not yield the saturated dimer.

[5] This yield is based upon the diene, which has been used as diluent as well as reactant, and hence in large molar excess (2.5:1).

[6] Carbon-hydrogen analyses were performed by the Scandinavian Microchemical Laboratory, Copenhagen, Denmark.

anticipated for the ion $C_{14}H_{16}^{+}$. Consistent with a cagelike structure is the fact that the parent peak at 184 is several times more intense than any other peak in the spectrum.

Evidence for the saturated character of this molecule includes its inertness to bromine and potassium permanganate and its failure to consume hydrogen over Adams' catalyst in acetic acid containing perchloric acid. Moreover, there is no absorption corresponding to carbon-carbon double bond stretching in the infrared spectrum, and the lack of end absorption in the ultraviolet spectrum excludes beyond doubt the presence of unsaturation.

Structures III and IV, derived in a formal sense by the coupling of two norbornadiene nuclei via the termini of their homoconjugated diene systems, can be eliminated through consideration of the infrared and proton magnetic resonance spectra of the 165° dimer. The former taken in carbon tetrachloride has maxima at 3.37, 3.49, 6.90, 7.62, 7.73, 8.10, 8.16, 8.46, 9.30, 10.51, and 11.51μ. Incidentally, this and the Nujol mull spectrum are both relatively simple, a fact consistent with a highly symmetrical structure. With regard to III and IV, there is no band in the 12.3-12.5μ range (a region in which many tricyclenes and nortricyclenes show prominent absorption), nor is there a band characteristic of cyclopropane derivatives in the 9.8-10μ region. More compelling is the absence of a carbon-hydrogen stretching frequency below 3.37μ[7] and the lack of absorption in the n.m.r. spectrum at higher field than 8.2τ.[8]

The most cogent evidence we can adduce for structures I, heptacyclo-

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[7] L.J. Bellamy, The Infrared Spectra of Complex Molecules pp. 17, 29, 30. John Wiley, New York (1959).

[8] J.A. Pople, W.G. Schneider and H.J. Bernstein, High Resolution Nuclear Magnetic Resonance pp. 236, 237. McGraw-Hill, New York (1959); G.V.D. Tiers, Characteristic Nuclear Magnetic Resonance 'Shielding Values' for Hydrogen in Organic Structures. Minnesota Mining and Manufacturing Company, St. Paul, Minnesota (1958).

(5.5.1.1.$^{4,10}0.^{2,6}0.^{3,11}0.^{5,9}0.^{8,12}$)-tetradecane, or II, heptacyclo-(7.4.1$0^{2,8}0.^{3,7}0.^{4,12}0.^{6,11}0^{10,13}$)-tetradecane, is provided by the high resolution n.m.r. spectrum. In pyridine at 60 mc the spectrum consists of two sharp, symmetrical peaks at 7.55τ and 8.21τ corresponding to methine and methylene protons, respectively.[8] As expected, the intensity ratio is 3.1. No fine structure is discernible in either peak under conditions of optimum resolution, whether the solvent be pyridine or carbon tetrachloride.

It is possible to conceive of other saturated structures for $C_{14}H_{16}$ which are not rigorously excluded by the data outlined above, but to our knowledge all are derivable from norbornadiene only via highly improbable pathways. Since structure II possesses a center of symmetry lacking in I, it was conceivable that a decision between them could be reached by determination of the probable space group through single crystal X-ray examination (i.e. unit cell considerations alone might demand that the molecule possess a center of symmetry.) If this proved not to be the case, X-ray diffraction studies could distinguish I and II only through complete structure elucidation. The determination of the probable space group has not as yet been successful because virtually all of the crystals we have examined have been twinned.[9]

The thermal stability of the cagelike dimer merits comment. Vapor of this substance in a stream of nitrogen has been passed through a Pyrex tube packed with Pyrex helices and heated to temperatures in excess of 500°, and the major portion of the dimer has crystallized unchanged in the cooler part of the pyrolysis tube.

In summary, the low adsorbability, high volatility, relatively high

[9] L. deVries and S. Winstein, J.Amer.Chem.Soc. 82, 5363 (1960), have encountered similar problems with the birdcage hydrocarbon, crystals of which are "highly disordered."

melting point, chemical inertness, and thermal stability of the 165° dimer are indicative of its cagelike character. Infrared, n.m.r., ultraviolet, and mass spectral data powerful support structure I or II, but permit no distinction between them.

Acknowledgements - It is a pleasure for us to acknowledge the kindness of Mr. Seymour Meyerson of the American Oil Company who measured the mass spectrum of the 165° dimer and of Mr. Kenneth Kawano who determined the n.m.r. spectra. The X-ray photographs were taken by Professor Lawrence Dahl who, like Professor Peter Yates, has offered valuable suggestions. We are grateful also for financial assistance from the National Science Foundation.

1961

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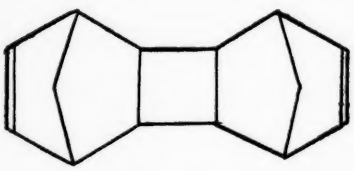
DIMERIZATION OF BICYCLOHEPTADIENE BY METAL CARBONYLS

C.W. Bird, D.L. Colinese, R.C. Cookson, J. Hudec and R.O. Williams

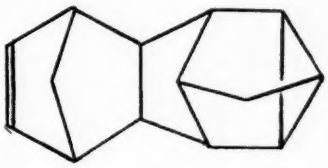
The University, Southampton

(Received 14 June 1961)

REACTION of [2:2:1]-bicycloheptadiene with iron pentacarbonyl, di-iron nonacarbonyl, tri-iron dodecacarbonyl or dicobalt octacarbonyl gives similar mixtures of metal-free products from which we have isolated in a pure state five ketones[1] and four dimeric hydrocarbons (two more dimers are produced by nickel tetracarbonyl[1]). From chemical and spectroscopic evidence we formulate the dimer melting at 68.5-69° (20% yield) as the endo-trans-endo isomer of structure (I) (nickel carbonyl yields the exo-trans-exo isomer,[1] m.p. 92-93°). One liquid dimer (8% yield), containing a bicycloheptene and a nortricyclene unit, has structure (II); another liquid dimer (1% yield) may be the other stereoisomer of II, although other possibilities are not excluded. But probably the most remarkable product is the highest-melting dimer (m.p. 163-164°, yield 4%), easily separated because it is the first



I



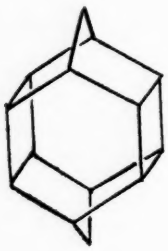
II

[1] C.W. Bird, R.C. Cookson and J. Hudec, Chem. & Ind. 20 (1960); R.C. Cookson, R.R. Hill and J. Hudec, Ibid. 589 (1961).

to be eluted from a column of silica gel.[2]

This dimer (Found: C, 91.11; H, 8.70; M.W. in freezing benzene, 179. $C_{14}H_{16}$ requires: C, 91.25; H, 8.75; M.W., 184) is saturated by the usual chemical tests and is almost transparent down to 200 mμ. The infra-red spectrum, which is relatively simple, has no band where cis double bonds usually absorb and also lacks the bands at 3100 and 800-815 cm^{-1} usually characteristic of nortricyclenes. The stability to strong acid makes the presence of a nortricyclene group even more unlikely, and the possibility of a hydrogen atom on a cyclopropane ring in the molecule is eliminated by the absence of proton resonance at fields higher than 8.3τ. In fact the proton resonance spectrum (kindly measured by Dr. L. Pratt) consists of only two unresolved peaks at 7.62 and 8.24τ, in the ratio of 3:1, corresponding to tertiary and secondary protons.

Neglecting structure involving extensive and improbable rearrangements, we must consider two possible formulations of the saturated dimer: two molecules of the monomer might unite face to face to give III, or at right angles to one another to give IV. The dimer was quite unchanged by passage



III

IV

[2] This dimer has also been made by Dr. Lemal and Mr. Shim, whom we thank for their courtsey in agreeing to this simultaneous publication of results.

through a silica tube at 500° with a contact time of 30 sec. This stability to heat, and the lack of splitting in the resonance signal from the tertiary protons under high resolution, while not entirely excluding III, do argue strongly in favour of IV.

The dimer (IV) is formed, with the other products, when bicycloheptadiene is boiled with iron pentacarbonyl in light, but it is also formed (in about the same yield) with di-iron nonacarbonyl at room temperature in the dark. The ability of light to induce this reaction with iron pentacarbonyl may, then, depend merely on its well known promotion of loss of carbon monoxide to give the more reactive monacarbonyl.[3]

We acknowledge an I.C.I. Fellowship (to J.H.) and support by the U.S. Air Force (Geophysics Research Directorate, A.R.D.C.) through its European Office.

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[3] J. Dewar and H.O. Jones, Proc.Roy.Soc. A 79, 66 (1906).

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THE STRUCTURE OF GRINDELIC ACID, A NEW DITERPENE ACID

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Istituto di Chimica Organica dell'Universita, Roma

(Received 2 June 1961)

AN INVESTIGATION on the chemical constitution of the resin[1] from Grindelia robusta is at present in progress in this Institute. In this preliminary communication we wish to report the first results obtained from the examination of the fraction containing water-insoluble, light petroleum soluble acids.[2]

Methylation of these with diazomethane gave a mixture of esters that we have been able to separate into several components by means of chromatography on alumina. The principal component, eluted with light petroleum-ether 9:1, was a colourless, crystalline solid, m.p. 70-70.5° (from methanol), $[\alpha]_D$ = -134.1° (in methanol), with a molecular formula $C_{21}H_{34}O_3$(I).[3] By mild hydrolysis with N potassium hydroxide it afforded an acid $C_{20}H_{32}O_3$(II) m.p. 100-101° (from acetic acid), $[\alpha]_D$ = -102.2°, to which we have given the name "grindelic acid". With diazomethane, it again produced ester (I).

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[1] The present knowledge on the chemical constitution of the resin from Grindelia robusta is based upon an old work of F.B. Power and F. Tutin, which reports that this resin consists mainly in unidentified liquid unsaturated acids [Chem.Zentr. I, 1401 (1908)].

[2] Our starting material was a commercial dry hydro-alcoholic extract of the plant.

[3] Satisfactory analyses were obtained for all compounds reported. Melting points were determinated on a Kofler block and have not been corrected. Ultra-violet measurements were made on ethanol solutions. Specific rotations were determined on chloroform solutions (unless otherwise indicated) at room temperature.

The majority of degradation experiments were made upon methyl ester (I), which was more easily obtained and purified. It was unsaturated, giving a positive reaction with tetranitromethane and with potassium permanganate. Catalytic hydrogenation of (I) in the presence of platinum oxide at atmospheric pressure yielded liquid saturated dihydrogrindelic acid methyl ester $C_{21}H_{36}O_3$ (III).

Grindelic acid methylester (I) failed to give the reactions of alcohols and carbonyl compounds. It had no marked light absorption above 210 mμ; the ethylenic bond and ester group were not in conjugation. The infrared spectrum of (I) (in Nujol) showed no hydroxyl band, only one carbonyl band at 1740 cm^{-1} (unconjugated ester), a band at 1095 cm^{-1}, which could probably be assigned to a five- or six-membered ring ether, and a low intensity band, missing in dihydroester (III), at 835 cm^{-1}, which made the presence of a trisubstituted double bond in (I) very probable.

All these data permitted the hypothesis that grindelic acid might be a bicyclic diterpene unsaturated acid, with an ether bridge and with the carboxyl group in a sterically unhindered position.

At the first confirmation of this hypothesis, selenium dehydrogenation of the ester (I) gave 1,2,5-trimethylnaphthalene, characterized as its 1,3,5-trinitrobenzene adduct.

On high pressure and high temperature hydrogenation with a palladium-charcoal catalyst, methyl grindelate (I) afforded, beyond the dihydroester (III), a small but significant quantity of a saturated hydrogenolized ester. Its infra-red spectrum showed a hydroxyl band, but the ether band at 1095 cm^{-1} had disappeared. This latter was missing also in the product obtained by refluxing ester (I) with acetic anhydride. On the contrary, dihydroester (III) was stable in the same conditions. A probable allylic nature of ether bridge in (I) was deduced.

In the attempt to find support for this hypothesis the next reactions on ester (I) were made. Reduction with lithium aluminium hydride gave liquid primary alcohol $C_{20}H_{34}O_2$ (IV) (I.R. bands at 3390, 1105, 835 cm^{-1}). Reduction of the latter with lithium in anhydrous ethylamine proceeded very smoothly, giving diol $C_{20}H_{36}O_2$ (V) m.p. 104-105°, $[\alpha]_D$ = +86.6°. Its I.R. spectrum showed a hydroxyl band, but did not show the bands at 1105 and 835 cm^{-1}. The double bond was accordingly shifted into a tetrasubstituted position.[4]

When catalytically reduced (platinum oxide in acetic acid), the diol (V) gave a saturated diol $C_{20}H_{38}O_2$ (VI), m.p. 121-122°, $[\alpha]_D$ = +28.5°. It was not an α-glycol, because it did not react with lead tetraacetate. Oxidation of (VI) with chromic acid in acetone[5] and then methylation with diazomethane gave an oily hydroxy-ester $C_{21}H_{38}O_3$ (VII) (I.R. bands at 3510 and 1735 cm^{-1}). One of the hydroxyl groups of (VI) was accordingly tertiary.

Dehydration of the hydroxy-ester (VII) with phosphoryl chloride in ice-cold pyridine afforded a mixture of unsaturated esters, among which a conjugated isomer predominates. This, isolated by chromatography on aluminium oxide, was a liquid with the composition $C_{21}H_{36}O_2$ (VIII). Its infra-red spectrum showed bands at 1720 cm^{-1} (conj. ester) and at 1645 cm^{-1} (conj. double bond). In ultra-violet, it had an absorption maximum at 221 mμ (log ε = 4.17). The ester (VII) must consequently be a tertiary β-hydroxyester.

This was confirmed by ozonolysis of (VIII) (in ethyl acetate at -60°), which produced a liquid ketone that was identified as the known 15,16-bis-norlabdan-13-one (IX) by its infra-red spectrum and by formation of 2,4-dinitrophenylhydrazone $C_{24}H_{36}O_4N_4$, m.p. 144-145° and of semicarbazone $C_{19}H_{35}ON_3$, m.p. 187-188° $[\alpha]_D$ = +32.6°.[6] As a further confirmation, hypoiodite

[4] A.S. Hallsworth et al., J.Chem.Soc. 1969 (1957).

[5] A. Bowers, T.G. Halsall and E.R. Jones, J.Chem.Soc. 2555 (1953).

[6] J.D. Cocker and T.G. Halsall, J.Chem.Soc. 4262 (1956).

oxidation of (IX) gave iodoform and an acid $C_{17}H_{30}O_2$ m.p. 140-141.5°, $[\alpha]_D$ = +42.3°, identified as 14,15,16-trisnorlabdanoic acid (X).[6]

The compounds (V), (VI), (VII), (VIII), (IX) and (X) must consequently have the structure reported in Chart 1.

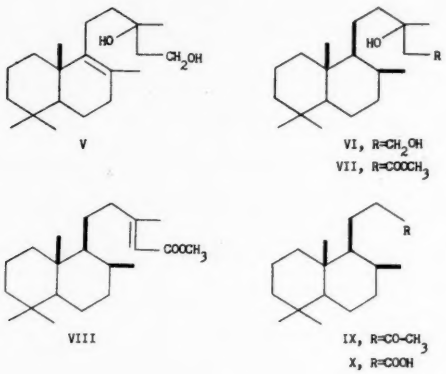

Chart 1.

The carbon skeleton and a good part of the structure of grindelic acid were clarified in this way. In the attempt to establish the position of the double bond, and consequently the attack point of the ether bridge in allylic position, ester (I) was submitted to oxidation with osmium tetroxide in ether-pyridine, from which a dihydroxy-ester $C_{21}H_{36}O_5$ (XI), m.p. 122-123°, $[\alpha]_D$ = +19° was obtained. On cleavage with lead tetraacetate in benzene, dihydroxy-ester (XI) gave oily keto-aldehyde (XII) (I.R. bands at 2705, 1740, 1720, 1700 cm^{-1}), which by chromic acid oxidation and then by esterification with diazomethane was transformed into keto-diester $C_{22}H_{36}O_6$ (XIII), m.p. 102-103° (I.R. bands at 1740 and 1700 cm^{-1}). This proved that the double bond of methyl grindelate was actually in a trisubstituted position.

If we assume the ether ring to be five- or six-membered, the only possible position of the double bond are 9.11 or 7.8. The failing of Lieben reaction on keto-ester (XIII) made the former more probable, but this

was not found to be the case.[7]

In fact, the attempt to hydroxylate the double bond of (I) by Woodward procedure[8] produced the unsaturated monohydroxy-ester $C_{21}H_{34}O_4$ (XIV), m.p. 115-116°, $[\alpha]_D = -105.3°$. Its infra-red spectrum showed bands at 3425 cm^{-1} (hydroxyl), 1740 cm^{-1} (ester carbonyl) and 1645 cm^{-1} (double bond).[9]

The fact that an allylic primary alcohol group was present in (XIV) was proved by manganese dioxide oxidation[10] of the hydroxy-ester.

When this reaction was made in the absence of oxygen a liquid αβ-unsaturated aldehydo-ester (XV) was obtained, characterized as 2,4-dinitrophenylhydrazone $C_{27}H_{36}O_7N_4$, m.p. 166-168° (λ_{max} 372 mμ; log ε = 4.53). The infra-red spectrum of (XV) showed bands at 2705, 1740, 1695, 1640 cm^{-1}. The ultra-violet spectrum had an absorption maximum at 227 mμ (log ε = 4.03).

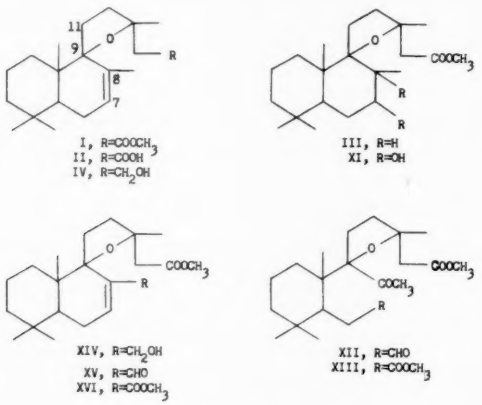

Chart 2.

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[7] It is known that sterically indered methyl-ketones may fail to give Lieben reaction.

[8] Advances in Organic Chemistry Vol. I, p. 137. Interscience, New York (1960).

[9] An analogous case of allylic oxidation is reported by L.H. Briggs, B.F. Cain and B.R. Davis [Tetrahedron Letters No. 17, 9 (1960)].

[10] R.M. Evans, Quart.Rev. 13, 61 (1959).

When the reaction was allowed to take place in the presence of oxygen, an acid was obtained that by action of diazomethane gave αβ-unsaturated ester $C_{22}H_{34}O_5$ (XVI) m.p. 58-59°, $[\alpha]_D = -96.6°$ ($\lambda_{max} = 211$ mμ; log ε = 3.75. I.R. bands at 1740, 1725, 1640 cm^{-1}). The double bond of (I) must consequently be located in the 7.8 position and the ether bridge must be five-membered. Therefore grindelic acid had structure (II) (chart 2).

In terms of stereochemistry, the obtaining of (IX) and (X) from ester (II) showed that the rings in grindelic acid were trans-fused and that $C_{(10)}$methyl was β-oriented. Research to establish the configuration at $C_{(9)}$ and $C_{(13)}$ is in progress.

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THE STRUCTURE OF THE MACROLIDE ANTIBIOTIC FILIPIN[1,2]

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and

J. N. Shoolery and L. F. Johnson

Varian Associates, Palo Alto, California

(Received 14 June 1961)

The fungicidal antibiotic filipin[3] belongs to a rather large class of polyene macrolides, only two members of which - pimaricin[4] and lagosin (II)[5] - have so far been attributed structural formulae. We should now like to report evidence which permits the assignment of expression I to filipin, the only uncertainty being the exact termination point of the lactone as expressed by the bracket in I. Filipin, therefore, possesses either a twenty-nine or thirty-membered lactone ring and represents the largest macrolide which has so far been encountered in nature.

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[1] Macrolide Antibiotics XI. For paper X see A. J. Birch, E. Pride, R. W. Rickards, P. J. Thompson, J. D. Dutcher, D. Perlman, and C. Djerassi, Chem. & Ind. 1245 (1960).

[2] Supported by grant No. 2G-682 from the National Heart Institute and grant No. A-4257 from the National Institute of Arthritis and Metabolic Diseases of the National Institutes of Health, U. S. Public Health Service.

[3] G. B. Whitfield, T. D. Brock, A. Ammann, D. Gottlieb, and H. E. Carter, J. Am. Chem. Soc. 77, 4799 (1955).

[4] J. B. Patrick, R. P. Williams, and J. S. Webb, J. Am. Chem. Soc. 80, 6689 (1958).

[5] M. L. Dhar, V. Thaller, and M. C. Whiting, Proc. Chem. Soc. 310 (1960).

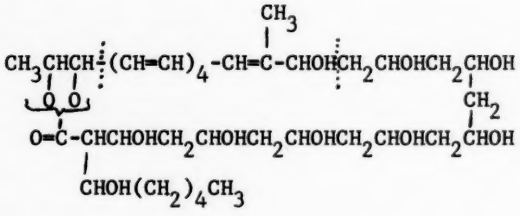
The presence of the masked glycol grouping (isolation of acetaldehyde by periodate cleavage after lactone opening), the hydroxylated hexyl fragment on the carbon atom adjacent to the lactone carbonyl group (isolation of hexanal by base-promoted retroaldolization) and the location of a methyl group at one end of the pentaene chromophore (isolation of 2-methylhendecanedioic acid upon nitric acid oxidation of perhydrofilipin) have already been established in our earlier communication.[6] The direct attachment of the polyene carbon sequence to the glycol moiety is shown by the observation that the longest wavelength maximum (λ_{max} 355 mμ)[3] of the pentaene chromophore of filipin (I) is moved to 386 mμ upon opening of the lactone ring and cleavage with sodium metaperiodate in buffered solution, the bathochromic shift being due to conjugation of the newly generated carbonyl function with the five double bonds.

We have reinvestigated in greater detail the earlier reported[6] nitric acid oxidation of perhydrofilipin, in particular the steam-nonvolatile dibasic acid fraction. Analytical and preparative gas phase chromatography of the methyl esters followed by mass spectrometric analysis[7] gave the following

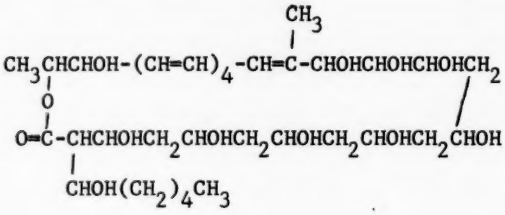
[6] B. Berkoz and C. Djerassi, Proc. Chem. Soc. 316 (1959).

[7] While the details will be published subsequently, the following brief comment is pertinent. The mass spectra of α-branched dicarboxylic acid esters have not yet been discussed in the literature, but by utilizing the experience of R. Ryhage and E. Stenhagen, Arkiv Kemi 14, 497 (1959) for straight chain analogs and considering the empirical rules for fragmentation (J. H. Beynon, "Mass Spectrometry", Elsevier, Amsterdam, 1960, pp. 329 et sequ.) one can use the following approach. In unbranched methyl esters, one of the principal cleavages occurs between the α and β carbon atoms to give M-73 and m/e 74 (rearrangement of one hydrogen). In α-methyl ones, fragmentation occurs predominantly at the branched carbon to yield M-87 and m/e 88. The relative ratios of M-73 vs. M-87 and peaks 74 vs. 88 can, therefore, be very instructive and the validity of this analysis has been checked with mixtures of authentic esters.

results. The first six peaks (split in an analytical column) consisted of the homologous series dimethyl succinate to dimethyl azelate, each acid containing an approximately equal amount of the corresponding α-methyl analog (e.g. peak 1: dimethyl succinate plus dimethyl α-methylsuccinate). Peak 7 constituted dimethyl 2-methyldecanedioate containing only about 10% of dimethyl decanedioate, while the largest peak, No. 8, contained no unbranched acid but only dimethyl 2-methylhendecanedioate contaminated with a small amount of the next higher homolog, dimethyl 2-methyldodecanedioate. It follows, therefore, that the principal mode of attack by nitric acid upon perhydrofilipin occurs between the two broken lines in I. When perhydrofilipin was first subjected to lactone opening and periodate cleavage, followed by nitric acid oxidation, gas phase chromatography and mass spectrometric analysis revealed the same pattern of dibasic acids except that the largest peak was now dimethyl 2-methyldodecanedioate. This requires that the non-methylated end of the polyene fragment be joined to the glycol grouping (as in I), since if the reverse arrangement had obtained, peak No. 8 (dimethyl 2-methylhendecanedioate) would again have been the largest one.



I



II

Originally,[3] a $C_{30}H_{50}O_{10}$ formulation had been proposed for filipin, but we pointed out[6] that a $C_{33}H_{54}O_{10}$ composition[8] would be in better agreement with the degradative evidence then available. Subsequently, Dhar et al.,[5] who had encountered similar difficulties in establishing a correct empirical formula for lagosin (II) and had settled the question eventually in favor of $C_{35}H_{58}O_{12}$ by X-ray crystallographic means, suggested that filipin should be represented by $C_{35}H_{58}O_{11}$ because of the similarities of the infrared spectra of the two antibiotics.

Five repeat analyses on carefully purified and dried filipin samples gave results (Table 1), which were in substantial agreement with those encountered earlier.[6] These did not distinguish between the empirical formulae $C_{35}H_{58}O_{11}$ and $C_{37}H_{62}O_{12}$, but they did seem to make $C_{33}H_{54}O_{10}$ less likely.

As will be shown below, a distinction between these formulae is of crucial importance as it settles automatically the structure of the antibiotic. This has now been accomplished by resorting to nuclear magnetic resonance spectroscopy.

Filipin peracetate, obtained by acetic anhydride - pyridine acetylation and chromatography on neutral alumina or

[8] Due to a misprint this was given in the text as $C_{33}H_{56}O_{10}$.

TABLE 1

	$C_{33}H_{54}O_{10}$	$C_{35}H_{58}O_{11}$	$C_{37}H_{62}O_{12}$	Found (Average of 5 Determinations)
C	64.89	64.20	63.57	63.99
H	8.91	8.93	8.95	8.82
O	26.20	26.88	27.47	27.23

silica gel, was dissolved in deuterochloroform and its N. M. R. spectrum measured with a Varian HR-60 spectrometer operating at 60 mc in a magnetic field of 14,092 gauss. Tetramethyl silane was added as an internal reference standard and peak positions are reported in δ units,[9] with δ increasing for decreasing magnetic field. A complex group of peaks was found in the region between δ = 6.81 and 4.23 which is assigned to the nine olefinic protons, the protons on the same carbon atoms as an acetate group, and the proton on the same carbon as the lactone oxygen. A triplet centered at δ = 2.92 is attributed to the proton adjacent to the lactone carbonyl function. The acetate methyl groups fall in a very strong peak which shows some fine structure at δ = 2.01. The methyl group attached to the doubly-bonded carbon appears at δ = 1.83, while the C_5H_{11} side chain gives peaks at δ = 1.22 and 0.86 for the CH_2 and CH_3 groups respectively.

The area of the peaks lying between δ = 6.81 and 4.23 was obtained in carbon tetrachloride solution by electronic integration using a digital voltmeter for accurate measurement. Similar determinations yielded the areas of all of the remaining protons. Since all of the olefinic protons, protons

[9] See C. Djerassi, T. Nakano, A. N. James, L. H. Zalkow, E. J. Eisenbraun, and J. N. Shoolery, J. Org. Chem. 26, 1192 (1961). $\delta = 10^6 \times \Delta\nu/60$, where $\Delta\nu$ is the frequency separation (in cps) of the tetramethyl silane reference peak and the peak being measured.

on the same carbon atom as acetate groups, and the proton attached to the same carbon as the lactonic oxygen are assigned to the 6.81 to 4.23 region, the ratio of the two areas represents an index of the number of acetate groups in filipin peracetate. For $C_{33}H_{54}O_{10}$ octa-acetate ($C_{49}H_{70}O_{18}$), the ratio of the larger to the smaller area (52/18) has a theoretical value of 2.88; for $C_{35}H_{58}O_{11}$ nona-acetate ($C_{53}H_{76}O_{20}$) it is 3.00, while for $C_{37}H_{62}O_{12}$ deca-acetate ($C_{57}H_{82}O_{22}$) it amounts to 3.10. The experimentally found value in ten separate determinations was 3.12 ± 0.02, which is only consistent with a deca-acetate $C_{57}H_{82}O_{22}$ and hence a $C_{37}H_{62}O_{12}$ empirical formula for filipin.

The reliability of this conclusion is dependent upon the purity of the acetate, incomplete acetylation affording a higher ratio, while a lower one would be obtained if partial dehydration had intervened. Therefore as a check, lagosin (II)[5,10] was acetylated and purified under exactly the same conditions as had been employed for filipin and the peracetate subjected to N. M. R. acetyl determination. Since the empirical formula of lagosin had been established by X-ray means,[5] complete acetylation must yield a deca-acetate, corresponding to $C_{55}H_{78}O_{22}$, whose predicted ratio of the total protons less the low-field protons to the low-field protons is 58/20 = 2.90. The results of ten measurements gave 2.92 ± 0.02, thus demonstrating the reliability and accuracy of our procedure. It should be noted that if lagosin (II) had been acetylated incompletely to a nona-acetate, the predicted ratio would have been 3.00, while if dehydration had occurred, it would have been 2.52.

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[10] We are indebted to Dr. M. C. Whiting of Oxford University for a gift of lagosin (II).

It should be pointed out that an alternate N. M. R. criterion can be used to arrive again in favor of the empirical formula $C_{37}H_{62}O_{12}$ for filipin (I). The number of protons in the region δ = 6.81 to 4.23 includes nine olefinic protons and the remainder depends upon the number of $-CHOC-$ groups. The complex multiplet resulting from all of these protons appears to break into two groups of peaks on either side of the point δ = 5.46 (328 cps from tetramethyl silane). If the assumption is made that the nine olefinic protons in the conjugated chain lie between 5.46 and 6.81, then the ratio of the area between 5.46 and 4.23 to the area (5.46 - 6.81) representing these nine protons yields another indication of the molecular formula of filipin peracetate. For $C_{49}H_{70}O_{18}$ it is 9/9 = 1.00; for $C_{53}H_{76}O_{20}$ it is 10/9 = 1.11; while for $C_{57}H_{82}O_{22}$ (deca-acetate of $C_{37}H_{62}O_{12}$), it is 11/9 = 1.22. The value found in four separate determinations was 1.19, which again is only consistent with the last empirical formula.

We have noted earlier[6] that filipin does not possess any vicinal glycol groupings aside from the one where the lactone ring terminates. Filipin does not contain any primary hydroxyl groups as evidenced by several unsuccessful attempts to prepare a trityl ether of either filipin or perhydrofilipin. Consequently, all remaining oxygen atoms must be represented by secondary hydroxyl functions each separated from the next one by at least one methylene group. This requirement, combined with the empirical formula $C_{37}H_{62}O_{12}$ and the other structural features enumerated above, can only be accomodated in expression I. Biogenetically, filipin follows the acetate pattern, but the origin (propionate, formate, etc.) of two of the C-methyl groups remains to be determined. Tracer experiments to settle this point are contemplated.

Thanks are due to the Upjohn Company, Kalamazoo, Michigan, for the supply of filipin and certain analytical determinations, and to Mr. E. Meier of the Stanford University Microanalytical Laboratory for the latest microanalytical determinations.

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THE DIRECT OXIDATIVE CONVERSION OF 2-METHYLTRYPTOPHAN TO 4-ACETYLQUINOLINE

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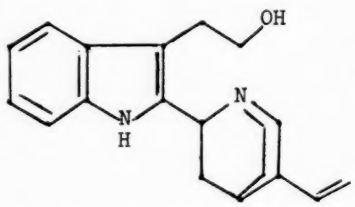
Department of Chemistry, University of Wisconsin

Madison, Wisconsin

(Received 19 June 1961)

THE structural similarity between cinchonamine (I) and cinchonine (II) leads



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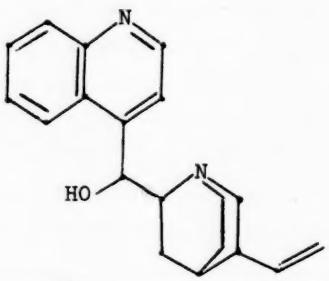

II

to the indisputable conclusion that these two alkaloids are biochemically related,[1] and hypothetical schemes which assume production of the quinoline from the indole base have been roughly outlined by previous authors.[1,2,3]

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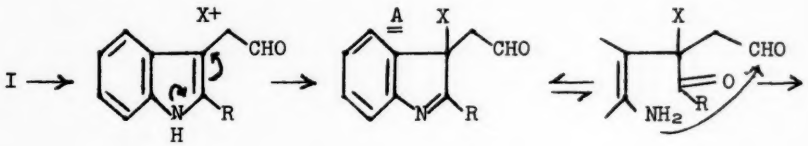
[1] R. Goutarel, M.-M. Janot, V. Prelog and W.I. Taylor, Helv.Chim.Acta 33, 150 (1950).

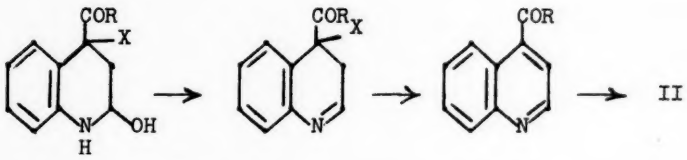
[2] R. Robinson, The Structural Relations of Natural Products p. 122. Oxford University Press, London (1955).

[3] B. Witkop, Abstracts of the Fourth National Medicinal Chemistry Symposium of the American Chemical Society, June 17-19, 1954, p.90.

The particular interpretation which served as a working hypothesis for the present investigation may be expressed as sequence (A) (R = vinyl quinuclidine residue),[4,5] where X+ most likely represents the agent OH^+ or an equivalent. In considering the feasability of duplicating the essentials



IIIa



of this sequence in the laboratory, we entertained the idea of oxidizing 2-methylindole-3-acetaldehyde (IIIb), a model for the suggested intermediate IIIa. Inspection of the literature revealed that the required simple aldehyde might be prepared by controlled oxidation of 2-methyl tryptophan (IV), with sodium hypochlorite, presumably by way of operation (B);[6]

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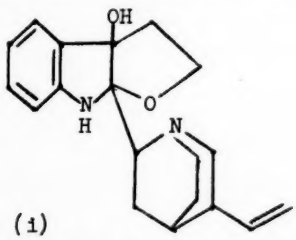
[4] The exact nature and chronological order of steps must be considered uncertain, and the scheme set forth should not be taken to indicate any preference in this regard.

[5] The natural occurrence of quinamine (i) constitutes support for the

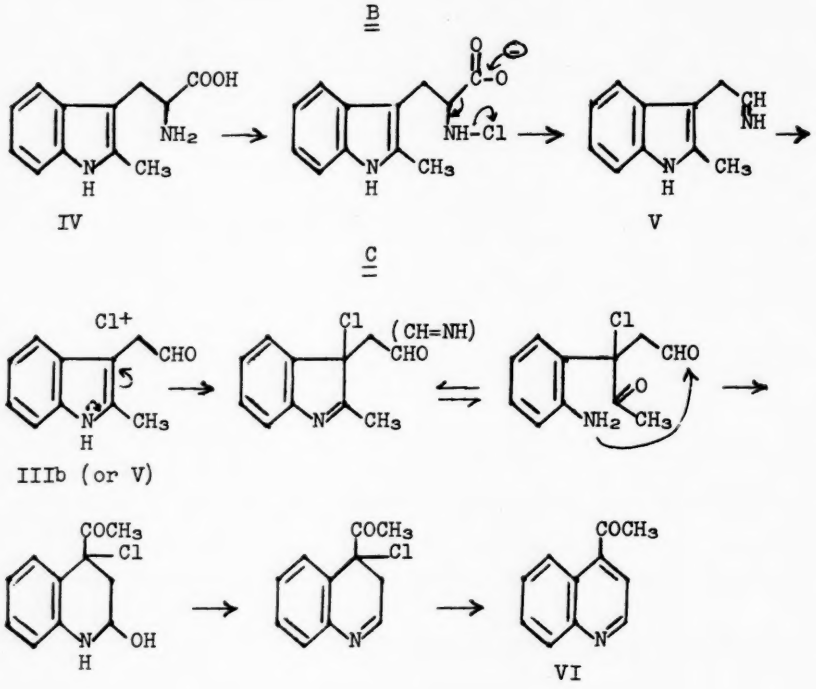


(i)

proposed electrophilic attack at C-3 in cinchonamine.

[6] R.A. Gray, Arch.Biochem.Biophys. 81, 480 (1959).

and the method brought to mind the possibility of carrying out, with this same reagent, not only conversion (B), but the sequence (C) as well, a close parallel to the biosynthetic speculation (A). Accordingly, 2-methyltryptophan was warmed (50°) for a short time with <u>two</u> <u>equivalents</u> of alkaline



hypochlorite (supplied as commercially available Chlorox), under which conditions 4-acetylquinoline (VI)[7] was produced in approximately 20% yield. We regard this overall transformation as proceeding through the individual stages just suggested (B and C), in which case the discrete, consecutive

[7] Identified by comparison (I.R., U.V. and m.m.p.'s of picrates and 2,4-dinitrophenylhydrazones) with an authentic specimen.

chemical steps carried out in one reaction vessel total seven, as a minimum. Insofar as can be perceived from the available literature, this oxidative rearrangement (IV ⟶ VI) is the first example of its kind, and we are currently assessing the potentiality of this type of change.

The authors are grateful to the National Institutes of Health for financial support (RG-3892).

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1961

THE STRUCTURE OF LOGANIN

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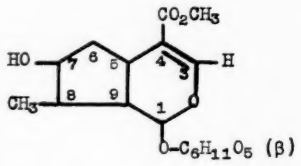
(Received 19 June 1961)

IN this communication we wish to report that loganin ($C_{17}H_{26}O_{10}$), a glycoside isolated from Strychnos nux-vomica[1,2,3] and other Strychnos species,[4,5] has the constitution represented by formula (I).



I

The glucosidic nature and the presence of one additional free hydroxyl group in loganin, m.p. 222-223°,* as suggested by previous investigators,[2,4] was confirmed by the production of glucose on enzymatic hydrolysis with

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* This loganin was isolated from the fruit pulp of Strychnos nux-vomica. The authors are thankful to S.B. Penick and Company, and to Mr. Shanti Sheth, Bombay, for supplying the pulp.

1 W.R. Dunston and F.W. Short, Pharm.J.Trans. 14, 1025 (1883).

2 K.W. Merz and K.G. Krebs, Arch.Pharm. 275, 217 (1937).

3 K.W. Merz and H. Lehmann, Arch.Pharm. 290, 543 (1957).

4 A.J. Birch and E. Smith, Austr.J.Chem. 9, 234 (1956).

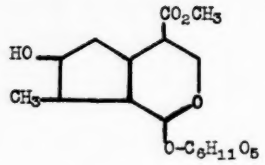
5 A.J. Birch and J. Grimshaw, J.Chem.Soc. 1407 (1961).

emulsin and by the formation of a pentaacetate derivative, m.p. 139-140°.

Loganin consumed one equivalent of sodium hydroxide on heating and gave methanol and norloganin, m.p. ca. 110°, λ_{max} 234 mμ (ε 9360), characterized as its penaacetate derivative, m.p. 99° and 160-162°, λ_{max} 231 mμ (ε 12,300). Norloganin displayed a broad, weak band at 2500-2700 cm^{-1} characteristic of the hydrogen-bonded hydroxyl group of a carboxylic acid. The sodium salt of norloganin lacked a carbonyl peak at 1695 cm^{-1}, but showed new peaks at 1522 and 1380 cm^{-1} which are assigned to a carboxylate anion. The fact that loganin is the methyl ester of norloganin was deduced from the formation of loganin pentaacetate by the action of diazomethane on norloganin pentaacetate.

The presence of an enol-ether group conjugated with the carbomethoxyl function in loganin was indicated by bands in the infrared at 1722 cm^{-1} ($-CO_2CH_3$) and 1660 cm^{-1} (-C=C-O-) and by absorption in the ultraviolet at 236 mμ (ε 10,940). This structural feature was confirmed by the facile uptake of one equivalent of hydrogen by the use of platinum oxide as a catalyst and acetic acid as a solvent. Dihydrologanin (II), m.p. 160-162°, does not absorb in the ultraviolet above 210 mμ and lacks the enol-ether band at 1660 cm^{-1}.

Diagnostically, the two most significant signals in the NMR spectra of loganin and loganin pentaacetate, determined at 56.4 mc in deuterium oxide and carbon tetrachloride respectively and related to tetramethylsilane as a standard, proved to be the ones at -470 and -56 c.p.s. The former is assigned to the conjugated olefinic proton at C-3 and the unusually large shift to lower magnetic field confirms the location of the oxygen atom of the enol-ether as adjacent to it. The signal at -56 c.p.s., appearing as a doublet, is assigned to a single methyl group spin coupled with an adjacent proton. It should be noted that similar peaks are exhibited by verbenalin.



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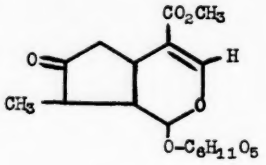

III

The presence of a pyran ring finds support from a comparison of the ultraviolet spectrum of loganin with model compounds[6,7] and with the spectra of the closely related verbenalin,[8] genepin,[9] asperuloside,[10] and plumieride.[11] The presence of a furan ring is excluded since it would be expected to absorb at 251 m ,[12] higher than the values of 234-237 m found for loganin and its derivatives.

The placement of the glucose radical at C-1 was deduced from the positive Tollens and 2,4-dinitrophenylhydrazine reactions given by the aglycone (R_f 0.85*) of loganin (R_f 0.48) and the aglycone (R_f 0.81) of dihydrologanin (R_f 0.45).

Of the remaining four carbon atoms, one of which is a methyl group, three must take the form of another ring since the presence of a second double bond is eliminated by the hydrogenation data and by ozonolysis experiments with loganin and its derivatives, which all gave trace amounts

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* Solvent system: butanol-acetic acid-water (4:1:1), paper: Whatman No. 1.

6 L.N. Owen, J.Chem.Soc. 385 (1945).

7 F. Korte and K. Buchel, Ber. 92, 877 (1959).

8 G. Buchi and R.E. Manning, Tetrahedron Letters No. 26, 5 (1960).

9 C. Djerassi, T. Nakano, A.N. James, L.H. Zalkow, E.J. Eisenbraun and J.H. Shoolery, J.Org.Chem. 26, 1192 (1961).

10 J. Grimshaw, Chem. & Ind. 403 (1961).

11 O. Halpern and H. Schmid, Helv.Chim.Acta 41, 1109 (1958).

12 F. Korte, K. Buchel, D. Scharf and A. Zschocke, Ber. 92, 884 (1959).

of formaldehyde but no other carbonyl compounds. The three carbon atoms are attached in the form of a cyclopentane ring at C-5 and C-9 and the methyl group is located at C-8 for biogenetic reasons.

Oxidation of loganin by the Jones procedure[13] yielded a crystalline ketone (III), $C_{17}H_{24}O_{10}$, m.p. 189-191°, which displayed absorption at 234 mμ (ε 11,100) and 1650, 1700 and 1751 cm^{-1} (cyclopentanone). The fact that the hydroxyl groups of the glucosyl radical were not affected was indicated by the formation of glucose on hydrolysis with emulsin. The ketone (III) was stable toward traces of sodium methoxide and sodium carbonate and was not identical with verbenalin. The low intensity $n-\pi^*$ transition in the ultraviolet spectrum of (III), $\lambda_{max}^{H_2O}$ 290 mμ (ε 44) as compared with $\lambda_{max}^{H_2O}$ 290 mμ (ε 160) for verbenalin suggests that the carbonyl group in (III) is located at C-7 and that loganin is best represented by formula (I).

Structure I is also consistant with the formation of succinic, methyl succinic and oxalic acids by alkaline permanganate oxidation of the aglycone of loganin.

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[13] K. Bowden, I.M. Heilbron, E.R.H. Jones and B.C.L. Weedon, J.Chem.Soc. 39 (1946).

Tetrahedron Letters No. 12, pp. 398-403, 1961. Pergamon Press Ltd. Printed in Great Britain.

196

A METHOD FOR EXPLORING THE DIPOLAR CHARACTER OF TRANSITION STATES. A GENERAL DIRECTING EFFECT OF POLAR SUBSTITUENTS IN OLEFIN ADDITION REACTIONS

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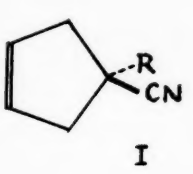
(Received 17 May 1961; in revised form 12 June 1961)

THE study of the direction of addition of reagents to unsymmetrically substituted open chain olefins has a long history, but until recently,[1] very much less information has been available concerning the effects of substituents on the direction of addition of reagents to cyclic olefinic bonds in a plane perpendicular to the initial double bond. Cyclopentenes, substituted at C_4 (cf. I), provide some of the simplest compounds for the evaluation of such perpendicular directing effects,[1] addition occurring either cis or trans to the potentially directing substituent. 4-Cyanocyclopentenes (I; R = H and Me) have been prepared; their reactions with peracid and with acetyl hypobromite show that the substituent at C_4 can strongly influence the direction of addition to the olefinic bond. In order to find out if a nitrile group would exert an effect across two or more saturated rings, related tricyclic (III) and bicyclic (II; R = H and Me) compounds

[1] Summary of recent work given by H.B. Henbest, B. Nicholls, W.R. Jackson, R.A.L. Wilson, N.S. Crossley, M.B. Meyers and R.S. McElhinney, Bull.Soc.Chim.Fr. 1365 (1960).

have been synthesized. These molecules are flat in general shape due to the trans fusion of rings and, as with the monocyclic compounds (I), differences from a 50:50 cis:trans ratio of products provide a measure of the directing effect of the polar substituent.



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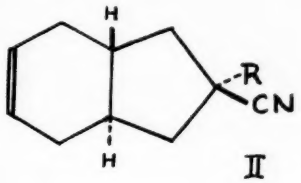

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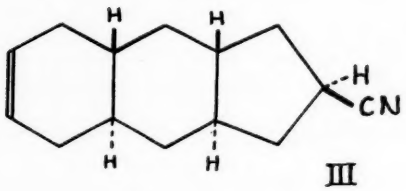

III

The olefin-peracid reaction is a simple addition in that the simultaneous or subsequent attack of a nucleophilic species upon the reacting carbon-carbon bond is not involved. The reaction can be carried out in a wide variety of solvents and, kinetically, is first order in olefin and in peracid. A spiro, chelated structure has been plausibly proposed[2] for the transition state, but for the moment, the simplified expression, (δ+) olefin -- O•O(H)COR (δ-), will be used; substituent effects show that the reacting carbon-carbon bond becomes electron deficient during the reaction.[2]

Good yields (85-95%) of epoxide mixtures were obtained from reactions of the olefinic nitriles (I, II, III) with pure perlauric acid in cyclo-

[2] Lynch and Pausacker, J.Chem.Soc. 1525 (1955); references to earlier work are given in this paper.

pentane and in acetonitrile (chosen to represent non-polar and polar solvents respectively). Analysis (gas chromatography for the mono- and bi-cyclic compounds, adsorption chromatography for the tricyclic compound) of each of the total reaction products gave the following cis:trans ratios of epoxy-nitriles.* Possible percentage errors in the ratios are ± 1-2% for the mono- and bi-cyclic compounds, and ± 2-3% for the tricyclic compound. The ratios were not altered by moderate changes in concentrations of reactants, and separate experiments showed that the epoxides were not isomerised under the reaction conditions. The cis:trans ratios represent therefore the relative rates of reaction of the peracid at each face of the molecule.

cis : trans Ratios of Epoxy-nitriles from Reactions of Unsaturated Nitriles with Perlauric Acid at 20°

	Reaction in cyclopentane	Reaction in acetonitrile
	cis:trans ratio	cis:trans ratio
Hydrogen series (R = H		
I	5:95	24:76
II	31:69	46:54
III	43:57	53:47
Methyl series (R = Me)		
I	13:87	48:52
II	28:72	45:55

* The individual cis- and trans-epoxy-nitriles have been isolated, each being a crystalline compound with the exception of (±)-4β-cyano-1α, 2α-epoxy-4α-methylcyclopentane. Configurations are assigned from dipole moment values and other evidence. [The product from the bicyclic nitrile (II; R = H), previously thought (H.B. Henbest and B.Nicholls, Proc.Chem.Soc. 225 (1958)) to be the cis-compound, has been shown to be a mixture of both isomers, the dipole moments of the pure cis- and trans- compounds being 4.78 D. and 2.49 D. respectively. We thank Dr. L.E. Sutton and Mr. G.M. Glover (Oxford) for these measurements.]

In all but one case, the tricyclic nitrile in acetonitrile, the reactions gave predominantly trans-epoxy-nitriles. Two main trends can be seen in the results from the hydrogen series of compounds (I, II, III; R = H): the proportion of trans-epoxy-nitrile decreases (a) as the distance between the substituent and the reaction centre is made greater, and (b) when the solvent is changed from cyclopentane to acetonitrile. These facts are consistent with an intramolecular polar directing effect of the nitrile group, the relative sizes of the dipole-dipole interactions between the polar substituent and the polar transition states for cis- and trans-attack favouring the latter reaction (cf. IV). Such an electrostatic effect would diminish with distance and be diminished by the presence of surrounding polar acetonitrile solvent molecules. These arguments are supported by results from the reaction of perlauric acid with the bicyclic chloride (II; R = H; CN replaced by Cl). The experimental ratios, 33:67 in cyclopentane and 50:50 in acetonitrile, show that the chloride has a weaker directing effect than cyanide, in accord with the relative magnitudes of the dipole moments of these groups (C-Cl, 2.04 D.; C-CN, 3.61 D., when attached to secondary carbon).

An alternative reason for the prevalent trans-attack might be steric hindrance imposed by the substituent on the cis-reactions; but on this basis the solvent effect would be difficult to explain. However, replacement of hydrogen by methyl in the bicyclic series (II; R = Me) led to an increase in the amount of reaction trans to the nitrile (cis therefore to the methyl group). This result can hardly be explained on steric grounds, but it does fit the dipole-dipole interaction theory, as the methyl group, by its inductive effect, increases the effective dipole of the directing group;*

* The dipole moments of acetonitrile, propionitrile and isobutyronitrile are, for solutions in benzene, 3.48, 3.57 and 3.61 D.

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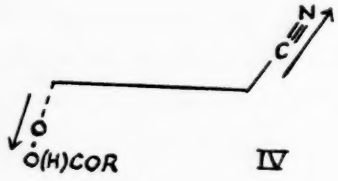
significantly also, the increase in the proportion of trans-product caused by the methyl group is greater in cyclopentane than in acetonitrile.



IV

Preferred transition state for olefin-peracid reaction

V

Preferred transition state for olefin-acetyl hypobromite reaction

In contrast, introduction of a 4-methyl group into 4-cyanocyclopentene causes a decrease in the proportion of attack trans to the nitrile group, showing that the alkyl group does exert a steric effect when it is closer to the reaction centre. Nevertheless, the polar directing effect of the 4-cyano-group (augmented by the electron donating effect of the methyl group) outweighs the steric effect of the methyl group in the epoxidation of compound (I; R = Me), especially in the non-polar solvent, cyclopentane. With the exception of these results with 4-cyano-4-methyl-cyclopentene, where the steric factor intrudes, the general trans directing effect of the nitrile (or chloride) group can be correlated with calculated potential energy interactions between the polar substituent and the polar transition states for cis and trans attack. The correlation will be discussed in the detailed papers on this subject.

A method thus becomes available for examining the dipolar nature of transition states of addition reactions in general. Its use in studying additions to carbonyl bonds is discussed in the following communication, but an extension to the work on the olefin-peracid reaction was provided by the addition of acyl hypohalites to the carbon-carbon double bond. Consider-

ation of possible transition states for these additions suggested that the main products from the unsaturated nitriles should be those, that on hydrolysis and ring closure under alkaline conditions, would lead to the production of cis-epoxy-nitriles. The nitriles (I and II; R = H) were treated successively with acetyl hypobromite in carbon tetrachloride and alkali to give epoxy-nitriles of cis:trans-composition 86:14 and 64:36 respectively. If partial bonding of both acetate and bromine groups to the original olefinic centre is postulated for the transition state for the addition step, it may be concluded that the preferred transition state (V) has its dipole in the direction indicated. This is in agreement with the polar character suggested[3] for the transition state of the diaxial to diequatorial rearrangement of steroid 2,3-bromo-acetates, which as a readdition reaction, is related to the initial diaxial addition of halogen and acyloxy groups.

The directing effects encountered in additions to carbonyl bonds (following paper), and in the addition of hydroperoxide anion to 3-oxo-Δ^4-steroids,[1] can also be explained in terms of intramolecular dipole-dipole interactions during the reactions.

Other electron attracting substituents also promote trans-attack of peracid at endocyclic and exocyclic double bonds. These results, together with further discussion of solvent effects, will be presented later.

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[3] D.H.R. Barton and J.F. King, J.Chem.Soc. 4398 (1958).

Tetrahedron Letters No. 12, pp. 404-409, 1961. Pergamon Press Ltd. Printed in Great Britain.

1961

POLAR AND SOLVENT EFFECTS IN THE REDUCTION OF SUBSTITUTED CYCLOHEXANONES*

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The Queen's University of Belfast, N.Ireland

(Received 17 May 1961)

THE direction of attack of the electrophilic reagent, perlauric acid, on olefinic bonds in cyclic compounds can be influenced by polar substituents, even when these are located across two or three saturated rings.[1] In order to determine the effect of a simple, linear dipolar substituent upon the direction of addition of a nucleophilic reagent to carbonyl bonds, we chose to study the reduction of chloro-cyclohexanones by borohydrides, the ketone-borohydride reaction usually being visualised as proceeding by intermolecular transference of hydride anions. Comparative experiments with the related reducing agents, diborane and lithium aluminium hydride, were also carried out.

Unhindered, alkyl substituted cyclohexanones react with complex hydrides to give equatorial alcohols as main products, for example, trans-4-methylcyclohexanol being formed in 80-84% yield on reduction of 4-methyl-

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* Some of the results reported in this paper were presented at the Conference on Stereochemistry held at the University of Alberta, Edmonton, September 1960.

[1] N.S. Crossley, A.C. Darby, H.B. Henbest, J.J. McCullough, B. Nicholls and M.F. Stewart, preceding paper.

cyclohexanone with lithium aluminium hydride.[2,3,4] The trans-4-methyl-alcohol is also the main product when the ketone is reduced with sodium borohydride (Table), but the proportion of trans:cis-methyl-alcohols depends upon the solvent. The solvent effects are not large, but it is noteworthy that the same order (yield of equatorial alcohol increasing in the sequence; methanol, tetrahydrofuran, isopropanol, acetonitrile) is observed in the reduction of 3-methylcyclohexanone, where cis-3-methylcyclohexanol is the major product. This dependence of product ratio upon solvent may be a steric effect, a reflection of the relative sizes of the solvation shells around each transition state. Further study is being made of this problem.

Results from the reduction of 4-chlorocyclohexanone show that the chlorine substituent has a considerable directing effect for, in contrast to the 4-methyl series, more cis- than trans- product was formed in each of four solvents; however, the relation between product ratio and solvent was different from that observed with the methyl-ketones. Preliminary experiments on the borohydride reduction of 12-oxospirostans show that a chlorine substituent at C_3 can exert a directing effect across the three saturated rings, the proportion of 12α-alcohol formed on reduction of the unsubstituted ketone being increased by 10-15% when a 3α- or 3β-chloro-group is present. These results, in conjunction with those of the mono-cyclic series, show that a chlorine substituent has the general effect of increasing the proportion of axial alcohol formed in reactions of cyclo-hexanones with borohydrides.

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[2] D.S. Noyce and D.B. Denney, J.Amer.Chem.Soc. 72, 5743 (1950).
[3] E.L. Eliel and R.S. Ro, J.Amer.Chem.Soc. 79, 5992 (1957).
[4] W.G. Dauben and R.E. Bozak, J.Org.Chem. 24, 1956 (1959).

Ratios of trans:cis-Substituted Alcohols formed in the Reduction of Substituted Cyclohexanones

	4-Methyl cyclohexanone	4-Chloro cyclohexanone	3-Methyl cyclohexanone
Sodium borohydride in			
methanol	82:18	41:59	17:83
tetrahydrofuran*	83:17	47:53	14:86
propan-2-ol	85:15	37:63	13:87
acetonitrile*	89:11	48:52	8:92
Equilibration in			
propan-2-ol	73:27**	55:45	77-79% cis (refs.3,4)
Diborane in			
tetrahydrofuran	89:11	31:69	8:92
Lithium aluminium hydride in			
tetrahydrofuran	84:16	33:67	85-92% cis (refs.2,3)

A similar, less pronounced, effect of the chlorine substituent was observed when the cis and trans-isomers of the 4-methyl- and 4-chloro-cyclohexanols were each brought to equilibrium in the presence of aluminium 2-propoxide. The same ratio of chloro-alcohols was obtained using either tetrahydrofuran[5] or the usual solvent, propan-2-ol. In the former solvent,

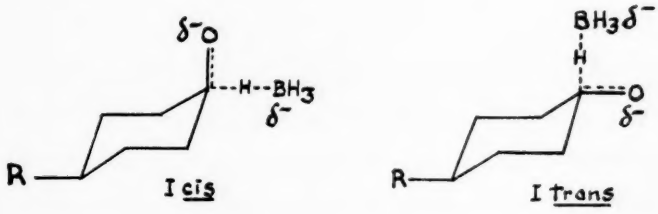
* Suspension of sodium borohydride in these solvents.

** W.G. Dauben and R.E. Bozak, preceding reference, give a ratio of 71:29.

[5] Equilibration of the chloro-alcohols occurred more quickly in tetrahydrofuran (than in propan-2-ol), and this solvent may therefore offer advantages for alkoxide-ketone interconversions in general.

the dominant species at equilibrium should be aluminium complexes of the chloro-alcohols. There would be a greater tendency for the free chloro-alcohols to be present in propan-2-ol, but since the chloro-alcohols can be expected to be more acidic than propan-2-ol, they may also be present as complexes to a large extent.

The effect of the chlorine substituent in changing the ratio of trans : cis-products in the reduction and equilibration experiments can be explained by intramolecular electrostatic interactions between the Cl-C_4 and C_1-O groups, such interactions being more favourable in structures related to the cis-chloro-alcohol than in those related to the trans-chloro-alcohol. Calculations, to be reported later, support this viewpoint of the results, one of the factors contributing to the increased stability of a cis-structure being the attractive force between its oxygen atom (in an axial position) and the electron deficient carbon at the 4-position; this attraction is greater with axial than with equatorial oxygen (in trans-structures) because of its smaller distance from C_4 (3.40 and 4.12 A respectively).



According to this interpretation of the results, the oxygen carries the greatest negative charge in the transition states of ketone-borohydride reactions; there is therefore an increased preference for the development of transition state (I cis) when R equals chlorine. The fact that a smaller proportion of cis-chloro-alcohol is obtained on equilibration of the alcohols than on reduction of the chloro-ketone suggests that the species

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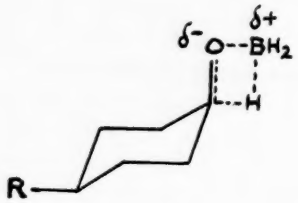
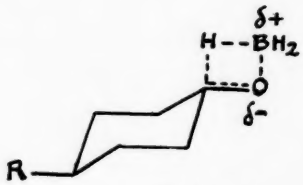
present, e.g., $ClC_6H_{10}OAl(OCHMe_2)_2$, at equilibrium are less polar (smaller δ- charge on oxygen) than are the transition states for ketone reduction, and this is in accord with their essentially covalent structures.



II cis



II trans

Ketones are reduced by diborane,[6] and this reagent gave even larger differences in isomer ratio when the reductions of 4-methyl- and 4-chloro-cyclohexanones were compared, the yields of cis-chloro-alcohol being 69 and 75% in tetrahydrofuran and dichloromethane respectively. Therefore these reactions also have polar transition states, the bulk of the δ- and δ+ charges probably being in the vicinity of the oxygen and the BH_2 groups (cf. II cis and trans).

Reduction of 4-chlorocyclohexanone with lithium aluminium hydride also gave a larger proportion of cis-product than from 4-methylcyclohexane, the trans : cis ratio being closer to that for diborane than that for boro-hydride reduction. This may be indicative of reduction proceeding by attack of aluminium hydride[7] rather than aluminohydride anions, but further experiments are required to decide this question. The reaction between 4-methoxy-

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[6] H.C. Brown, H.I. Schlesinger and A.B. Burg, J.Amer.Chem.Soc. 61, 673 (1939).

[7] D.M.S. Wheeler and J.W. Huffman, Experientia 16, 516 (1960), have suggested that aluminium hydride may be the active species in reductions of alkyl-ketones.

cyclohexanone and lithium aluminium hydride has been reported[8] to give a 70% yield of cis-4-methoxycyclohexanol. Although the methoxyl group is a bent dipole it exhibits therefore the same directing effect as chlorine in this reaction.

[8] D.S. Noyce, G.L. Woo and B.R. Thomas, J.Org.Chem. 25, 260 (1960).

Tetrahedron Letters No. 12, pp. 410-413, 1961. Pergamon Press Ltd. Printed in Great Britain.

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OPTICAL STABILITY OF A NINE-MEMBERED RING BRIDGED BIPHENYL[1]

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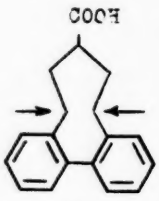
(Received 15 June 1961)

THE stereochemistry of 1,2,3,4-dibenzcyclonona-1,3-diene-7-carboxylic acid (I) is of considerable interest for several reasons. As revealed by a study of Dreiding models, interconversion of the enantiomeric forms requires that the molecule assume a transition state conformation in which



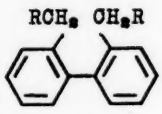
I

two hydrogens situated on C5 and C9 (arrows) suffer a maximum in non-bonded interaction; cogwheeling is precluded by the presence of the bridge. The effect of such interactions in rigid bicyclic structures has been a subject of recent concern.[2] In addition, extensive spectroscopic investigations

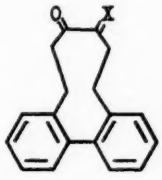
[1] Acknowledgment is made to the donors of The Petroleum Research Fund, administered by the American Chemical Society, for support of this research (PRF 422-A), and to the Alfred P. Sloan Foundation for fellowship support (K.M.).

into the relation between conjugation and conformation of 2,2'-bridged biphenyls[3] make it desirable to compare the U.V. spectrum of a simple nine-membered ring compound, e.g. I, with the well-known spectra of eight-, seven- and six- ring analogs.

Previous attempts at preparation of an appropriate compound have failed.[4] We now report the synthesis of I.



II a, R=COOH; b, R=CH_2COOH
c, R=CH_2COOCH_3; d, R=CH_2OH
e, R=CH_2Br; f, R=CH_2CN
g, R=CH_3



III a, X=O
b, X=N_2

Arndt - Eistert double chain-extension of IIa (m.p. 152-153°,[5] also obtained in a polymorphic form, m.p. 174-175° [Found: C, 70.84; H, 5.33; neut. eq., 142. $C_{16}H_{14}O_4$ requires: C, 71.10; H, 5.22; neut. eq., 135]) gave IIb, m.p. 160-161° [Found: C, 72.53; H, 6.20; neut. eq., 157. $C_{18}H_{18}O_4$ requires: C, 72.46; H, 6.08; neut. eq., 149]; methyl ester (IIc), polymorphic forms, m.p. 61-62° and 74.5-75.5° [Found: 73.52; H, 6.79. $C_{20}H_{22}O_4$ requires: C, 73.60; H, 6.79]. For large scale runs, IIb was most

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[2] L. de Vries and S. Winstein, J.Amer.Chem.Soc. 82, 5363 (1960); S. Winstein and R.L. Hansen, Ibid. 82, 6206 (1960); L. de Vries and P.R. Ryason, J.Org.Chem. 26, 621 (1961).

[3] G.H. Beaven, D.M. Hall, M.S. Lesslie and E.E. Turner, J.Chem.Soc. 854 (1952) et seq.

[4] G.H. Beaven, G.R. Bird, D.M. Hall, E.A. Johnson, J.E. Ladbury, M.S. Lesslie and E.E. Turner, J.Chem.Soc. 2709 (1955).

[5] J. Kenner and E.G. Turner, J.Chem.Soc. 2101 (1911); R. Weitzenböck, Monatsh. 34, 193 (1913).

conveniently prepared from IIa by $LiAlH_4$ reduction of the ethyl ester to IId, m.p. 88-89° [Found: C, 79.11; H, 7.32. $C_{16}H_{18}O_2$ requires: C, 79.31; H, 7.49], conversion to IIe, m.p. 48-49.5° [Found: C, 52.11; H, 4.19; Br, 43.37. $C_{16}H_{16}Br_2$ requires: C, 52.20; H, 4.38; Br, 43.42], with PBr_3 in benzene, conversion to IIf, m.p. 51-52° [Found: C, 82.97; H, 6.19; N, 10.59. $C_{18}H_{16}N_2$ requires: C, 83.04; H, 6.20; N, 10.76], with NaCN, and acid hydrolysis of IIf. Reductive ring closure of IIc with sodium in xylene yielded crude acyloin, oxidation of which with bismuth oxide gave IIIa, (25% overall yield from IIc) m.p. 202-203° [Found: C, 81.60; H, 6.09; mol. wt., 248. $C_{18}H_{16}O_2$ requires: C, 81.79; H, 6.10; mol. wt., 264]; quinoxaline derivative, m.p. 151-152° [Found: C, 85.78; H, 5.93; N, 8.71; mol. wt., 319. $C_{24}H_{20}N_2$ requires: C, 85.68; H, 5.99; N, 8.33; mol. wt., 336]. Treatment of the p-toluensulfonylhydrazone of IIIa with base gave diazoketone IIIb.

The photochemical Wolff rearrangement has been useful in ring contractions of classical[6] and of medium membered[7] rings. In the present case, IIIb was rearranged both thermally and photochemically (mercury source) (65%) to I, m.p. 137-138.5° [Found: C, 81.01; H, 6.68; mol. wt., 258. $C_{18}H_{18}O_2$ requires: C, 81.17; H, 6.81; mol. wt., 266]; p-toluide, m.p. 184-185° [Found: C, 84.69; H, 7.34; N, 4.19; mol. wt., 347. $C_{25}H_{25}NO$ requires: C, 84.47; H, 7.09; N, 3.94; mol. wt., 355]. The acid was optically activated by a second order asymmetric transformation[8] via the quinidine salt in

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[6] L. Horner and E. Spietschka, Chem.Ber. 88, 934 (1955); T.H. Colby, Ph.D. Dissertation, Univ.of Washington, 1957; W. Kirmse, Angew. Chem. 69, 106 (1957); W. Kirmse, L. Horner and K. Muth, Chem.Ber. 91, 430 (1958); M.P. Cava, R.L. Litle and D.R. Napier, J.Amer.Chem. Soc. 80, 2257 (1958); J. Meinwald and P.G. Gassman, Ibid. 82, 2857 (1960); Idem, Ibid. 82, 5445 (1960); J. Meinwald and E.G. Miller, Tetrahedron Letters No. 7, 253 (1961).

[7] L. Friedman, A. Rosegay and R.L. Litle, private communication.

[8] M.M. Harris in W. Klyne and P.B.D. de la Mare, Progress in Stereochemistry Vol. 2, p. 158. Academic Press, New York (1958).

acetone; the liberated acid had $[\alpha]_D^{28}$ - 48° (c 1.0, benzene) and racemized in o-xylene according to the expression $k_1 = 10^{12.5}e^{-24.0/RT}$ ($t_{0.5}^{50.0}$ 53 min). The optical stability of the molecule, which is chiefly the outcome of directed interaction between non-bonded hydrogens, is comparable to that of the corresponding seven-[9] and eight-[10] membered ring bridged biphenyls whose resistance to racemization is to a greater (and compensating) extent accounted for in terms of angle strain. A more quantitative discussion is reserved for the detailed paper.

In relation to the lower ring homologs, the biphenyl conjugation band of I [shoulder at 231 mμ (3.74)] has suffered a pronounced drop in extinction and a hypsochromic shift. The spectrum of I is markedly similar to that[11] of the open-chain analog IIg, including the long wave length features. Clearly, the angle of torsion in I has been significantly increased. The present work also firmly supports the view[12] that the assignment[13] of the 281 m band in phenyldihydrothebaine as a "diphenyl band" is in error.

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[9] D.C. Iffland and H. Siegel, J.Amer.Chem.Soc. 80, 1947 (1958).

[10] L.V. Dvorken, R.B. Smyth and K. Mislow, J.Amer.Chem.Soc. 80, 486 (1958).

[11] P.M. Everitt, D.M. Hall and E.E. Turner, J.Chem.Soc. 2286 (1956).

[12] D.M. Hall and F. Minhaj, J.Chem.Soc. 4584 (1957); cf. R. Robinson, Nature,Lond. 160, 815 (1947).

[13] E.A. Braude and W.F. Forbes, J.Chem.Soc. 3776 (1955).

Tetrahedron Letters No. 12, pp. 414-416, 1961. Pergamon Press Ltd. Printed in Great Britain.

A NOVEL AND CONVENIENT SYNTHESIS OF ARYLNORBORNYL CATIONS

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Department of Chemistry, Princeton University, Princeton, New Jersey (P.R.S.)

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(Received 30 June 1961)

BICYCLOHEPTADIENE (I) reacts with benzene and its derivatives in 97% sulfuric acid to form ions, the properties of which resemble those of α-monoaryl cations. Furthermore, the ions so formed are identical with those produced by the action of concentrated sulfuric acid upon corresponding 2-aryl (II)[1] and 1-arylnorbornanols (III and IV).[1] Cations from I, II, III, and IV exhibited the same ultraviolet spectra and possessed the same thermodynamic stabilities.

These ions, formulated as VII,[2] are probably formed from II directly, from III and IV by Wagner - Meerwein rearrangement and from I by alkylation to V and/or VI, followed by protonation and 6,2-hydride shift.[3] The cations

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[1] D.C. Kleinfelter, Ph.D. Thesis, Princeton University, 1960. For the synthesis of the arylnorbornanols (II-IV) see D.C. Kleinfelter and P. von R. Schleyer, J.Org.Chem. 26, In press (1961).

[2] N.C. Deno, to be published.

[3] L. Ruzicka in Perspectives in Organic Chemistry (Edited by A. Todd) p. 265. Interscience, New York (1956).

are presumably in equilibrium with hydrocarbons. Like 2-phenylbornyl cations,[4] ion VII (Ar = p-$CH_3OC_6H_5$) gave aryl hydrocarbons on addition of water; 2-p-anisylnorbornene was identified as the major product.

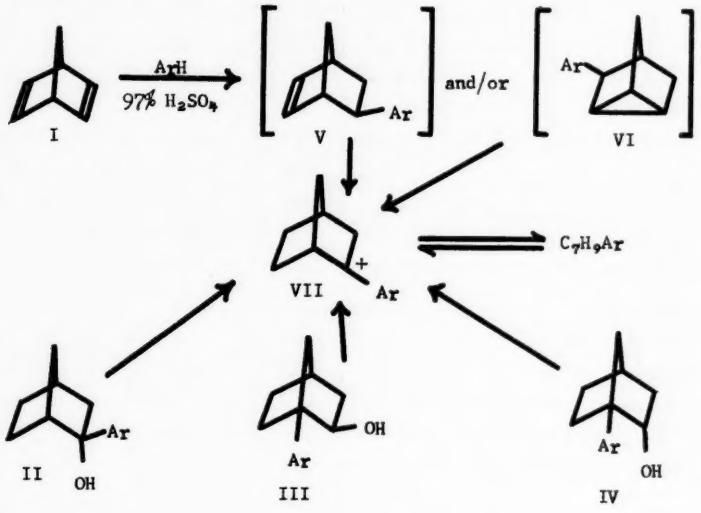

Table 1 summarizes values of λ_{max}, log e, and estimates of the % sulfuric acid at which the concentration of the cation equals concentration of the aryl hydrocarbons. From these latter values, pK_R^+ constants can be evaluated[4] and plotted against σ^+ substituent constants. The series Ar = C_6H_5, p-ClC_6H_4, p-$CH_3C_6H_4$ and p-$CH_3OC_6H_4$ give ρ about -6, a value similar to that of other aryl cation series.[2,4] These results are pertinent because of recent interest in the structure of monoaryl[1,2,4,5] and diaryl[1] bicyclo-[2,2,1]heptyl carbonium ions.

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[4] N.C. Deno, P. Groves, J. Jaruzelski and M. Lugasch, J.Amer.Chem.Soc. 82, 4719 (1960).

[5] P.D. Bartlett, E.R. Webster, C.E. Dills and H.G. Richey, Jr., Liebigs Ann. 623, 217 (1959); P.D. Bartlett, C.E. Dills and H.G. Richey, Jr., J.Amer.Chem.Soc. 82, 5414 (1960).

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TABLE 1. Stability and λ_{max} for 2-Arylbornyl Cations

Ar =	Cation prepared from	λ_{max} (mμ)	log e	H_2SO_4 %[a]
Phenyl	I,II,III,IV	337	4.58	76
4-Chlorophenyl	I,II,III,IV	365	4.59	77
4-Methylphenyl	I,II,III,IV	360	4.60	66
4-Methoxyphenyl	I,II,III,IV	381	4.69	45 ± 4
		369	4.55	
4-NH_3^+-phenyl	III,IV	327	4.23	92
4-$(CH_3)_2NH^+$-phenyl	II,III,IV	327	3.88	93
3-Methoxyphenyl	III	343	4.26	
2-Methoxyphenyl	II,III,IV	324	4.39	62
2,4-Dimethoxyphenyl	I	460		40 ± 5[b]
2,5-Dimethoxyphenyl	I	464		42[c]
3,4-Dimethoxyphenyl	I	433		40 ± 5[b]
2,4,6-Trimethylphenyl	I	408		72
2,4,6-Trimethoxyphenyl	I	430		40 ± 5[a]
		345		

[a] Acidity required for c_{R^+} = concentration of C_7H_9Ar.

[b] Cloudiness of the solutions in 0-45% H_2SO_4 prevented more precise estimation. These ions can be formed from I in acids as dilute as 75% H_2SO_4.

[c] This ion was unstable in the 42% H_2SO_4 region; this estimate may be in error.

Tetrahedron Letters No. 12, pp. 417-420, 1961. Pergamon Press Ltd. Printed in Great Britain.

TOXIC CONSTITUENTS OF "WHITE SNAKEROOT"

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Stanford, California

(Received 30 June 1961)

"Tremetol", the crude toxin responsible for "trembles" in cattle[1] and "milk sickness" in human beings[2] has been isolated from the "White Snakeroot" plant (Eupatorium urticaefolium) in 0.14-0.32% yield by the alcohol extraction procedure of Couch.[1] Partition chromatography (ligroin-95% MeOH) separated "tremetol" into a Sterol fraction (39%) and a Ketone fraction (61%). Alumina chromatography of the Sterol fraction yielded Terpene-I (15%, oil, $[\alpha]^{24}D$ +44.7° ($CHCl_3$), $C_{15}H_{24}$, Found: C, 88.35; H, 11.60; M.W. 205; Microhydrog., 1.84, 1.93 moles for M.W. 204), Sterol-I (32%, m.p. 184.5-185.5°, $[\alpha]^{24}D$ +57.2° ($CHCl_3$), $C_{30}H_{50}O$, Found: C, 83.8; H, 11.70; O, 4.43; M.W., 427), and Sterol-II (9%, m.p. 147-148°, $[\alpha]^{24}D$ -32.8° ($CHCl_3$), $C_{21}H_{34}O$, Found: C, 82.95; H, 11.52; O, 5.39; M.W. 314). In view of their non-toxicity to goldfish[3] these constituents have not yet been investigated structurally. The Ketone fraction was separated by alumina chromatography into "dehydrotremetone" (17%, m.p. 87.5-88.5°, opt. inactive, $C_{13}H_{12}O_2$, Found: C, 77.64; H, 6.30; O, 16.11; M.W., 207, C-Me, 13.40; oxime, m.p. 131-132°, $C_{13}H_{13}O_2N$, Found: C, 72.16; H, 6.13; N, 6.43), "tremetone" (48%, oil, $[\alpha]^{28}D$ -59.6° (EtOH), d^{28}_4 1.080, $n^{25}D$ 1.5658, $C_{13}H_{14}O_2$; semicarbazone, m.p. 222°,

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[1] J. F. Couch, J. Agric. Research 35, 547-576 (1927).

[2] J. F. Couch, J. Am. Med. Assoc. 91, 234 (1928).

[3] W. A. Gersdorff, J. Am. Chem. Soc. 52, 3440 (1930).

$[\alpha]^{28}D$ -56.2° ($CHCl_3$), $C_{14}H_{17}O_2N_3$, Found: C, 65.01; H, 6.61; N, 16.49; 2,4-dinitrophenylhydrazone, m.p. 183.8-184.2°, $C_{19}H_{18}O_5N_4$, Found: C, 59.50; H, 4.61; N, 14.57), and "hydroxytremetone" (3%, m.p. 70-71°, $[\alpha]^{24}D$ -50.7° (EtOH), $C_{13}H_{14}O_3$, Found: C, 71.29; H, 6.37; O, 21.77; M.W., 212; C-Me, 13.74; acetate, m.p. 89-89.5°, $C_{15}H_{16}O_4$, Found: C, 68.49; H, 6.20; O, 24.76). Since each of the ketones proved toxic to goldfish, tremetone, the most abundant constituent, was suspected of being the active toxin in "White Snakeroot" and was investigated structurally.

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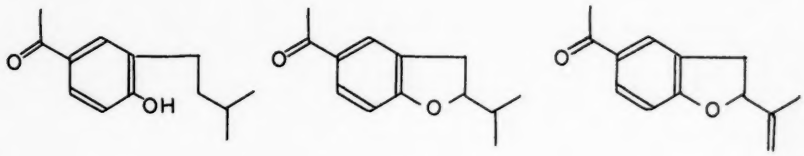
Reaction of tremetone with ozone yielded formaldehyde and with sodium hypoiodite iodoform, indicating the presence of methylene and acetyl functions. Catalytic hydrogenation of tremetone (Pd/C) yielded hydrotremetone (oil, $[\alpha]^{25}D$ -47.0° (EtOH), $C_{13}H_{16}O_2$; oxime, m.p. 91.5-93.5°, $C_{13}H_{17}O_2N$, Found: C, 71.20; H, 7.64; O, 14.39; N, 6.55; 2,4-dinitrophenylhydrazone, m.p. 181-184°; $C_{19}H_{20}O_5N_4$, Found: C, 59.25; H, 5.11; N, 14.64) and a phenolic ketone hydrogenolysis product whose oxime (m.p. 104.5-105°, $C_{13}H_{19}O_2N$, Found: C, 70.32; H, 8.70; O, 14.55; N, 6.32, C-Me, 11.8) and 2,4-dinitrophenylhydrazone (m.p. 202.5-203.5°, $C_{19}H_{22}O_5N_4$, Found: C, 58.80; H, 4.70; N, 14.66) indicated it to be $C_{13}H_{18}O_2$.

O-Methylation of the above phenolic ketone, followed by permanganate oxidation and esterification afforded methyl 4-methoxyisophthalate, m.p. 97.5-98.5° alone and on admixture with an authentic sample. Beckmann rearrangement of the oxime of the phenolic ketone, followed by hydrolysis of the resulting amide yielded acetic acid and 2-isoamyl-4-aminophenol (m.p. 118-119.5°, $C_{11}H_{17}ON$, Found: C, 72.52; H, 9.34; N, 7.71); diacetate, m.p. 90.5-91.5°, $C_{15}H_{21}O_3N$, Found: C, 68.21; H, 7.86; O, 18.39; N, 5.28), indicating the phenolic ketone hydrogenolysis product to be 2-isoamyl-4-acetylphenol (I). This conclusion plus the above evidence requires hydrotremetone to possess structure II and tremetone III.

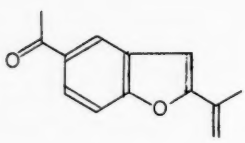


I II III

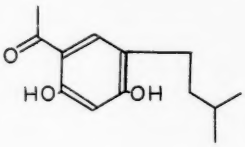
The structure I was confirmed by independent synthesis employing the sequence: phenol ⟶ phenyl isovalerate —(Fries)⟶ 2-isovalerylphenol (2,4-dinitrophenylhydrazone, m.p. 187-189°, $C_{17}H_{18}O_5N_4$, Found: C, 57.14; H, 4.91; N, 15.31) —(Clemmenson)⟶ 2-isoamylphenol (3,5-dinitrobenzoate, m.p. 86.5-87.5°, $C_{18}H_{18}O_6N_2$, Found: C, 60.03; N, 5.01; N, 7.80)⟶ 2-isoamylphenyl acetate —(Fries)⟶ I.

The structure II was confirmed by the synthetic sequence: salicaldehyde —($ClCH_2COCH_3$)⟶ 2-acetylbenzofuran —(1. CH_3MgI, 2. $-H_2O$)⟶ 2-isopropenylbenzofuran —(H_2-Pd/C)⟶ 2-isopropyl-2,3-dihydrobenzofuran —($(F_3CCO)_2O$-HOAc)⟶ racemic II (infrared spectra of oxime and 2,4-dinitrophenylhydrazone identical with those of hydrotremetone derivatives).

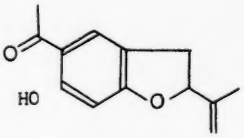
Structure III for tremetone was confirmed by several independent syntheses, the most convenient of which utilized the sequence: benzofuran-2-carboxylic acid —(Na-Hg)⟶ 2,3-dihydrobenzofuran-2-carboxylic acid ⟶ ethyl ester —(CH_3MgBr)⟶ 2-(2,3-dihydro-2-benzofuryl)-2-propanol —(Ac_2O-$SnCl_4$)⟶ 2-(5-acetyl-2,3-dihydro-2-benzofuryl)-2-propyl acetate —(pyrolysis)⟶ racemic III (separated chromatographically from other double bond isomers). After preliminary resolution of the intermediate 2,3-dihydrobenzofuran-2-carboxylic acid with (+)-amphetamine, the above sequence afforded a sample of tremetone which was identical in all respects with the natural product and which yielded crystalline derivatives similarly identical.



IV



V



VI

The structure of dehydrotremetone as IV was deduced from the observations that this ketone yielded formaldehyde on ozonization and produced on catalytic hydrogenation a sample of racemic hydrotremetone (II) whose infrared spectrum (and that of its oxime) was identical with that of the hydrotremetone (and oxime) obtained by the above reduction of tremetone.

Hydroxytremetone 1) yielded on O-acetate (m.p. 89-89.5°, Cf. above) which gave iodoform with hypoiodite and 2) produced a phenolic ketone (m.p. 92.5-94°, $C_{13}H_{18}O_3$, Found: C, 70.18; H, 8.12) on hydrogenolysis (Pd/C). The identity of this phenolic ketone as 2-isoamyl-4-acetylresorcinol (V) was established by comparison with an authentic sample produced by the sequence: resorcinol ⟶ 2-isovalerylresorcinol ⟶ 2-isoamylresorcinol ⟶ 2-isoamylresorcinol diacetate ⟶(Fries)⟶ V. These data require that hydroxytremetone possess structure VI. This conclusion has not yet been confirmed synthetically.

While quite lethal to goldfish, as might be anticipated from the similarities of their structures to that of the 2-isopropenyl-2,3-dihydrobenzofuran moiety of the rotenone molecule, the above ketones have not yet been established as toxic for higher animals.

The authors are indebted to the U.S. Public Health Service (NIH-RG-6232) for its generous support of this investigation.

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STRUCTURAL EFFECTS IN ELECTROPHILIC ALIPHATIC SUBSTITUTION REACTIONS OF ORGANOSILANES[1]

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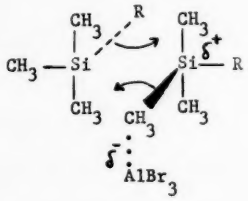
(Received 29 June 1961)

THE metal halide-catalyzed disproportionation of substituted tetraalkyl-

$$2\ RSi(CH_3)_3 \xrightarrow{Al_2Br_6} Si(CH_3)_4 + R_2Si(CH_3)_2$$

silanes is considered to involve electrophilic substitution on carbon and nucleophilic substitution on silicon.[2] The transition state is pictured as:



We have measured the initial rates of the forward step in the disproportionation of a number of alkyltrimethylsilanes in benzene solution at 40° by methods described previously.[2] Table 1 lists the relative rates of reaction observed for identical concentrations of reactants. In Table 1 the relative rates of a typical nucleophilic substitution ($R\text{-}I + I^{*-} \rightarrow R\text{-}I^{*} + I^{-}$) are also

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[1] Research sponsored by the National Science Foundation.

[2] G.A. Russell, J.Amer.Chem.Soc. 81, 4815, 4825, 4831 (1959).

given for comparison.[3]

TABLE 1

Relative Rates of Nucleophilic and Electrophilic Substitutions

R	Disproportionation of silanes at 40°*	Rate of iodide exchange**
allyl	71	42
ethyl	1.00	1.00
n-propyl	0.61	0.63
isopropyl	0.0048	0.038
n-butyl	0.15	0.42
isobutyl	0.025	0.059
cyclopentyl	0.059	0.046
cyclohexyl	0.0021	0.000007***

* 3.3 mmoles of silane, 1.8 mmoles of Al_2Br_6 in 5 ml of benzene (at 10°).
** Iodide exchange of RI in ethanol at 40°.
*** Extrapolated.

The similarity of structural effects in nucleophilic and electrophilic attack upon simple alkyl groups is obvious from Table 1. Fig. 1 demonstrates a more quantitative relationship. It seems unlikely that such a relationship could result from electrical effects since it might be expected that inductive effects would operate in opposite directions in S_N2 and S_Ei processes.[4]

Although transition states in S_N2 and S_Ei reactions have quite different geometry, with inversion of configuration in the S_N2 process and retention in S_Ei or S_E2,[5] it would appear that the data of Table 1 are best explained by

[3] H.A.C. McKay, J.Amer.Chem.Soc. 65, 702 (1943); H.Seelig and D.E. Hull, Ibid. 64, 940 (1942); S.F. Van Straten, R.V.V. Nicholls and C.A. Winkler, Canad.J.Chem. 29, 372 (1951); S. May, P. Daudel, J. Schottey, M. Sarraf and A. Vobaure, C.R.Acad.Sci.,Paris 232, 727 (1951).

[4] E.D. Hughes and C.K. Ingold, J.Chem.Soc. 244 (1935).

[5] S. Winstein, T.G. Traylor and C.S. Garner, J.Amer.Chem.Soc. 77, 3741 (1955); F.R. Jensen and L.H. Gale, Ibid. 81, 1261 (1959); H.B. Charman, E.D. Hughes and C.K. Ingold, J.Chem.Soc. 2523, 2530 (1959).

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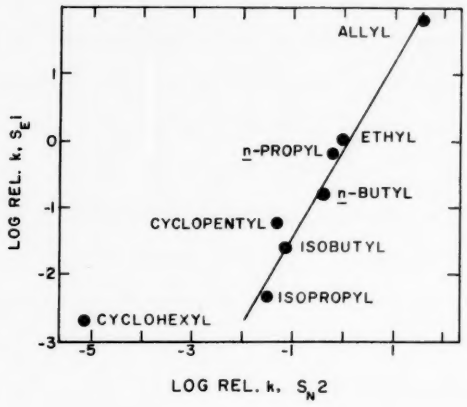

FIG. 1.

Free energy relationship between S_N2 and S_Ei reactions.

the conclusion that steric influences are the dominant effects in both reactions. The relationship displayed in Fig. 1 is as good as the average free energy relationship observed between different S_N2 processes. A similar conclusion is reached when the rates of cleavage of siliconalkyl bonds by strong acids are considered. The relative rates of cleavage of alkyltrimethylsilanes by hydrogen bromide-aluminum bromide in benzene at 40° are methyl$\gg$ethyl (1.00)$>$ n-propyl (0.13), n-butyl (0.17) isopropyl (0.04).

The deviation of cyclohexyl, and to a lesser extent cyclopentyl, from the straight line relationship of Fig. 1 are understandable when the extreme differences in the geometry of the transition states for substitution are considered. In the cyclohexyl system substitution by S_Ei or S_E2 process can occur without the entering or leaving group occupying the hindered axial position whereas in S_N2 processes both the entering and leaving group must

occupy sterically unfavorable positions. However, with these exceptions the transition states in the disproportionation of alkyltrimethylsilanes and exchange of iodide ion with alkyl iodides have nearly the same sensitivity to changes in size of the groups attached to the carbon atom undergoing attack. Electrical effects can also be important in S_Ei reactions as well as in S_N2 processes. For example, the relative rates of disproportionation of phenyl- or vinyl-trimethylsilane are approximately 30-50 times faster than ethyltrimethylsilane, a reactivity series quite different from that observed in S_N2 reactions. However, for simple alkyl groups the similarity of reactivities in S_N2 and S_Ei or S_E2 reactions indicates the unimportance of inductive effects in both processes.

Rate sequences similar to those of Table 1 have been observed in the cleavage of unsymmetrical dialkylmercury compounds by hydrogen chloride[6] and of alkylmercury iodides by hydronium ions.[7] In these cases the spread in reactivities is considerably less than in the disproportionation of tetraalkylsilanes and quite different rate sequences have been reported for cleavage reactions of symmetrical dialkylmercury compounds.[8] In the case of the alkyltrimethylsilanes any effect of a change in structure of the non-reacting alkyl group on the rate of reaction would be expected to be less important than a similar structural change in a cleavage reaction of a dialkylmercury compound.

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[6] M.S. Kharasch and A.L. Flenner, J.Amer.Chem.Soc. 54, 674 (1932); F.C. Whitmore and H. Bernstein, Ibid. 60, 2626 (1938).

[7] M.M. Kreevoy and R.L. Hansen, J.Amer.Chem.Soc. 83, 626 (1961).

[8] C.S. Marvel and H.O. Calvery, J.Amer.Chem.Soc. 45, 820 (1923); S. Winstein and T.G. Traylor, Ibid. 77, 3747 (1955); 78, 2597 (1956); R.E. Dessy, G.F. Reynolds and J.-Y. Kim, Ibid. 81, 2683 (1959); R.E. Dessy and Y.K. Lee, Ibid. 82, 689 (1960).

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THE SYNTHESIS OF 11,19-OXYGENATED PREGNANES FROM OUABAIN

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(Received 21 June 1961)

THE enhancement of biological activity of 11-oxygenated corticoids attending the introduction of oxygen at the C-18 methyl group, as exemplified by aldosterone,[1] has intensified interest in the isolation[2] and synthesis[3] of steroids oxygenated at the complementary C-19 methyl group. The author wishes to report a facile and practical conversion of the complex cardiac glycoside, ouabain,[4] to the hemi-ketal form (VII) of 19-hydroxy-4,5α-dihydro-11-dehydrocorticosterone and the hemi-ketal form (IX) of 19-hydroxy-5α-pregnane-3,11,20-trione.

Quabagenin-1,19-acetonide,[5] obtained readily from ouabain was oxidized with chromium trioxide and pyridine to the crude 3,11-diketone which when treated with a mixture of hot ethanol and basic alumina afforded the known 5α,14,19-trihydroxy-3,11-dioxo-5β-carda-1,20(22)-dienolide (I),[6] in an

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[1] L.F. Fieser and M.Fieser, Steroids pp. 701-708. Reinhold, New York (1959).

[2a] R. Neher and A. Wettstein, Helv.Chim.Acta 39, 2062 (1956); [b] G.W. Barber, D.H. Peterson and M. Ehrenstein, J.Org.Chem. 25, 1168 (1960).

[3a] G.W. Barber and M. Ehrenstein, J.Org.Chem. 19, 1758 (1956); [b] G.W. Barber and M. Ehrenstein, Ibid. 20, 1253 (1955) [c] G. Volpp, C. Baumgartner, and Ch. Tamm, Helv.Chim.Acta 42, 1408-1432 (1959); [d] G. Volpp and Ch. Tamm, Tetrahedron Letters No. 27, 31 (1960); [e] D.H.R. Barton and J.M. Beaton, J.Amer.Chem.Soc. 83, 750 (1961).

[4] L.F. Fieser and M. Fieser, ref. 1, p. 768

[5] C. Mannich and G. Siewert, Ber.Dtsch.Chem.Ges. 75, 737 (1942).

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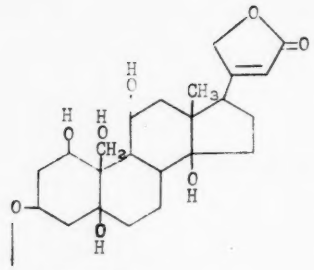
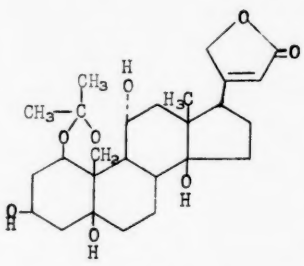
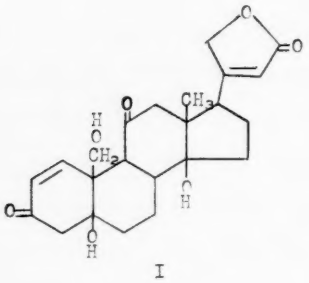


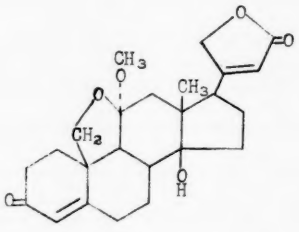
L-Rhamnosyl Ouabain



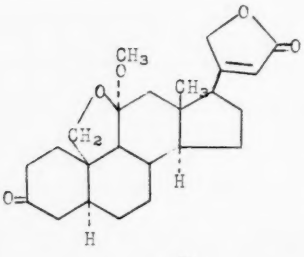
Oubagenin-1,19-acetonide



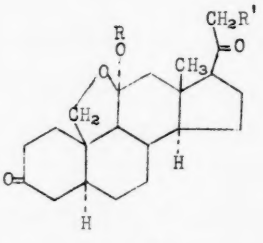
I



III



V



VI (R=CH_3, R'= OH)
VII (R=H, R'= OH)
VIII (R=CH_3, R'= H)
IX (R=H, R'=H)

improved overall yield of 55%. Hydrogenation of I over Pd-C in methanol

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[6] Ch. Tamm, Helv.Chim.Acta 38, 147 (1955).

gave 5β,11α,14-dihydroxy-11,19-epoxy-3-oxo-5β-card-20(22)-enolide (II), m.p. 178-181°, λ_{max}^{MeOH} 218 mμ (ε = 17,300) which is in equilibrium with 5β,14,19-trihydroxy-3,11-dioxo-5β-card-20(22)-enolide. After the catalyst is removed by filtration in the hydrogenation of I, direct treatment of the methanolic solution of II with a catalytic amount of p-toluenesulfonic acid yielded 14-hydroxy-11α-methoxy-11,19-epoxy-3-oxocarda-4,20(22)-dienolide (III), m.p. 258-260°, λ_{max}^{MeOH} 219 mμ (ε = 21,500), λ_{max}^{MeOH} 237 mμ (ε = 19,000), $[\alpha]_D$ + 149.8° $CHCl_3$), (C, 69.77; H, 7.30). Dehydration of III with thionyl chloride and pyridine afforded 11α-methoxy-11,19-epoxy-3-oxocarda-4,14,20(22)-trienolide (IV), m.p. 212-214°, $[\alpha]_D$ +119.5° ($CHCl_3$), (C, 72.43; H, 7.22). Hydrogenation of IV in the presence of Pd-C, ethyl acetate and methanol proceeded rapidly at a constant rate with the absorption of two equivalents of hydrogen to give in greater than 90% yield 11α-methoxy-11,19-epoxy-3-oxo-5α,14α-card-20(22)-enolide (V), m.p. 192-194°, λ_{max}^{MeOH} 217 mμ (ε = 15,000), $[\alpha]_D$ +126.5° ($CHCl_3$), (C, 72.33; H, 8.08). Ozonolysis of the unsaturated lactone in V and hydrolysis of the resulting 21-glyoxylic ester with aqueous methanolic potassium bicarbonate transformed V into 21-hydroxy-11α-methoxy-11,19-epoxy-5α-pregnane-3,20-dione (VI), m.p. 178-180°, $[\alpha]_D$ +134.5° ($CHCl_3$), (C, 70.43; H, 8.28). The overall yield from ouabain to VI was 18%. Hydrolysis of VI with aqueous acetone containing p-toluenesulfonic acid yielded 11α,21-dihydroxy-11,19-epoxy-5α-pregnane-3,20-dione (VII), m.p. 165-167°, $[\alpha]_D$ +107° ($CHCl_3$), (C, 69.70; H, 8.20). The p-toluenesulfonate of VI upon treatment with sodium iodide in acetone yielded the 21-iodo derivative which, when reduced with zinc in acetic acid, gave 11α-methoxy-11,19-epoxy-5α-pregnane-3,20-dione (VIII), m.p. 168-169°, $[\alpha]_D$ +145° ($CHCl_3$), (C, 73.05; H, 8.84). Hydrolysis of VIII afforded 11α-hydroxy-11,19-epoxy-5α-pregnane-3,20-dione (IX), m.p. 156-158°, $[\alpha]_D$ +103° ($CHCl_3$), (C, 72.98; H, 8.67). When VIII was dissolved in methanol containing a catalytic amount of p-toluenesulfonic acid, it was

converted to 3,3,11α-trimethoxy-11,19-epoxy-5α-pregnan-20-one (X), m.p. 111-112°, $[\alpha]_D$ +107° (MeOH), (C, 71.04; H, 9.18).

The optical rotatory dispersion curve of X,[7] which exhibits a positive Cotton effect, establishes the configuration of 17-acetyl group as β. The observations that X is not epimerized with warm 1N KOH in methanol and that the optical rotatory dispersion curve of V[8] exhibits a positive Cotton effect verify the conclusion that the product of the hydrogenation of IV has the A/B-*trans* and C/D-*trans* configuration.[9]

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[7] The author is most grateful to Dr. W. Klyne for providing the optical rotatory dispersion curve for compound X.

[8] The author is grateful to Dr. W.C. Wildman for providing the optical rotatory dispersion curve of V.

[9] In steroids containing a 14-iso(14β) configuration, the more stable configuration at C-17 is also iso (α) [*cf.* K. Meyer, *Helv.Chim.Acta* 30, 1976 (1947); A. Lardon, *Ibid.* 32, 1517 (1949); C.P. Balant and M. Ehrenstein, *J.Org.Chem.* 17, 1576 (1952)].

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STEREOCHEMISTRY OF FLAVAN-3,4-DIOLS

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(Received 17 June 1961)

THE stereochemistry of substituted flavan derivatives has been a more subtle and elusive matter than similar problems with saturated carbocyclic ring systems. This is mainly because the usual generalizations correlating reactivity and stereochemistry are not very reliable for a ring system containing a heteroatom and also aromatic unsaturation, features which conspire to produce unique complications.

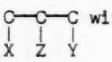
This note reports the application of nuclear magnetic resonance to the clarification of the molecular configurations of the two known flavan-3,4-diols which have been prepared from flavan-3-ol-4-one: (1) the flavan-3,4-diol m.p. 145° prepared by direct reduction of the 4-ketone[1] and (2) the flavan-3,4-diol m.p. 160° synthesized from the same ketone via the 4-oxime by reduction to the amine followed by nitrous-acid deamination.[2] Although both diols might be expected to have the same configuration at C_3, differing simply at C_4 as cis and trans diols, both can be converted to cyclic carbon-

[1] R. Bognár and M. Rákosi, Chem. & Ind. 188 (1956); Acta.Chim.Acad.Sci. Hung. 14, 369 (1958).

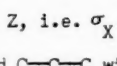
[2] R. Bognár, M. Rákosi, H. Fletcher, E.M. Philbin and T.S. Wheeler, Tetrahedron Letters No. 19, 4 (1959).

ates: diol m.p. 145° → carbonate m.p. 127-128° and diol m.p. 160° → carbonate m.p. 157-158°. That one of these carbonates is, in fact, a trans-derivative is revealed clearly by NMR.

Flavan-3,4-diol carbonate m.p. 127-128°. Two of the heterocyclic ring protons (X,Y) appear together coincidentally as a doublet at -332.6 and -322 c.p.s.[3,4] (relative intensity ca. 1:1.7). The resonance of the third heterocyclic proton (Z) occurs as a triplet at -268.6, -258 and -247.5 c.p.s. (relative intensities 1:1.1:0.5). The only other peaks in the spectrum are due to the aromatic protons at lower field; the integrated intensities over the spectrum are, aromatic: 9.1 protons, heterocyclic (X,Y): 2.0 protons and heterocyclic (Z): 1.0 proton. The X, Y and Z resonances constitute a unique and unexpectedly simple pattern which reveals that this is a very special case. There are only two possible ways in which the lines observed for the three heterocyclic protons might arise: (1) X, Y and Z are disposed



with X and Y having the same chemical shift and also the same coupling constant to Z, i.e. $\sigma_X = \sigma_Y$ and $J_{XZ} = J_{ZY} = 10.6$ c.p.s., and (2) X, Y and Z are disposed



with $\sigma_X = \sigma_Y$, J_{XY} finite and $J_{YZ} = 21.2$ c.p.s. (J_{XZ} expected to be <0.5 c.p.s.).[5] The second alternative clearly is not tenable since it demands a coupling constant which is far too large for protons

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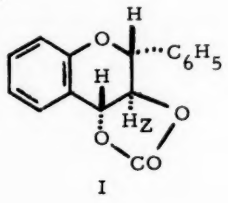
[3] Spectra were determined with a Varian 4300-B spectrometer in each case at 60 mc. Deuteriochloroform was used as solvent with tetramethylsilane as internal reference, solute concentration being in the range 10-15%. X, Y and Z refer to the proton resonances from low to high field respectively.

[4] All resonances expressed in c.p.s. from tetramethylsilane, negative values indicating lower field.

[5] This second and less obvious possibility represents a case which has not been recognized generally and which to our knowledge was first appreciated by Mr. J. Musher (Harvard Seminar, Feb. 1961). It is noteworthy that for this case the Z proton resonance will occur as a triplet even if $J_{XZ} = 0$ and $/\sigma_X - \sigma_Z/ = /\sigma_X - \sigma_Y/ =$ a very large value.

attached to adjacent carbons.[6] In the first and only remaining interpretation the H_Z-C-C-H_Y and H_X-C-C-H_Z torsional (dihedral) angles must both be ca. 180°,[6] a condition which unequivocally fixes the stereochemistry of the carbonate m.p. 127-128° as I (plus mirror image):



I

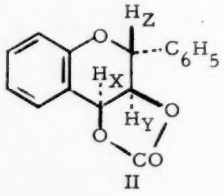
Scale models of I demonstrate that the three trans-hydrogens are rigidly axial in type. The power of NMR as a tool in stereochemical analysis is vividly illustrated by this example in which a single measurement defines clearly the interrelationship of three asymmetric centers.

The dibenzoate m.p. 156-157° which corresponds to the carbonate m.p. 127-128° and the diol m.p. 145° displays quite a different NMR spectrum with each of the three heterocyclic protons appearing individually: a doublet (X) at -403, -397.2 c.p.s., a pseudo-triplet (Y) (whose end-peaks faintly show signs of further splitting) center at -360 c.p.s. with flanks at ca. -366.5 and -353.5 c.p.s., and a doublet (Z) at -332.7 and -325.3 c.p.s. This spectrum indicates a C-C-C (X Y Z) system with J_{XY} = 5.8 c.p.s. and J_{YZ} = 7.3 c.p.s., clearly consistent with the all-trans hydrogen assignment that follows from I and, moreover, indicating that the strictly axial arrangement of C-H bonds as found in the carbonate I has been somewhat relaxed to permit more nearly normal bond angles and to relieve repulsion between adjacent

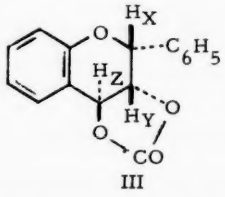
[6] See, for example, H. Conroy in Advances in Organic Chemistry Vol. II, pp. 308-311. Interscience, New York (1960); M. Karplus, J.Chem.Phys. 30, 6 (1959).

benzoyloxy groups.

Flavan-3,4-diol carbonate m.p. 157-158°. One of the three heterocyclic protons (X) exhibits resonance as a doublet at -337 and -331 c.p.s., and the remaining two (Y, Z) appear at higher field as a merged multiplet with four distinct peaks at -304.5, -294.5 (shoulder at low-field side), -288.7 (shoulder both sides) and -279 c.p.s. (shoulder at high-field side) (signal ratio ca. 1:3:9:1). The partial overlapping of the Y and Z resonances which causes the appearance of unresolved shoulders on some of the bands complicates the interpretation of the spectrum of Y and Z. A simple analysis proceeds as follows: (1) proton X might be coupled to either Y or Z with a coupling constant of roughly 6 c.p.s., (2) Y and Z are mutually coupled and from the intensity and separation of the two bands at -288.7 and -279 c.p.s. it appears that Z is coupled only with Y and that $J_{YZ} \sim 9$ c.p.s. and (3) from (1) and (2) the proton arrangement can be seen to be C-C-C with $J_{XY} \sim 6$ c.p.s. and $J_{YZ} \sim 9$ c.p.s. for consistency with the
X Y Z
observed spectrum. A more refined treatment following the general method of analysis for the ABX system[7] yields $J_{XY} = 6.4$, $J_{YZ} = 9.7$ and $|\sigma_Y - \sigma_Z| \sim 8$ c.p.s.; in addition the spectra derived by calculation[7] from values close



II



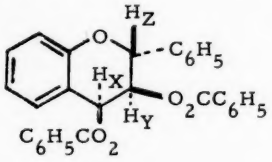
III

to these are in excellent agreement with that observed. These magnitudes of J_{XY} and J_{XZ} agree best with the assignments of stereoformula II (plus

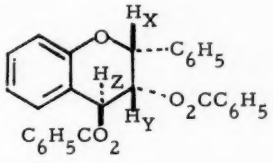
[7] J.A. Pople, W.G. Schneider and H.J. Bernstein, High-resolution Nuclear Magnetic Resonance Chap. 6. McGraw-Hill, New York (1959).

mirror image) for the carbonate m.p. 157-158°, for which the predicted coupling constants are $J_{XY} = 7$[8] and $J_{YZ} = 10$ c.p.s.,[6] but do not rigorously exclude the trans carbonate III (also less likely on chemical grounds). The alternative cis carbonate can be excluded on the basis that neither $J_{2,3}$ nor $J_{3,4}$ could reasonably be greater than 7 c.p.s.

The spectrum of the dibenzoate m.p. 121-122°, derived from flavan-3,4-diol m.p. 160° and in the same series with the carbonate m.p. 157-158°, adds strong support to the 3,4-cis, 2,3-trans arrangement of hydrogen, i.e. IV. The three heterocyclic protons occur as follows: one (X) a doublet at -398 and -401.5 c.p.s., a second (Y) as a quartet with peaks at -360, -356.5, -350 and -346.5 c.p.s. and the third (Z) as a doublet at -343 and -333 c.p.s. Simple analysis indicates the system C-C-C (X Y Z) with $J_{XY} = 3.5$ c.p.s., $J_{YZ} = 10$ c.p.s. and $|\sigma_Y - \sigma_Z| = 11.6$ c.p.s. These data are in disagreement with stereoformula V because the expected value of J_{XY} in V ($\sim$7 c.p.s.) is much greater than that observed.



IV



V

An independent argument in favor of II over III (or IV over V) is based on chemical shifts expected for these structures since the resonance of H_4 ought to occur at lower fields than the resonance of H_2 for both carbonate and benzoate. A definite proof of chemical shift assignments is desirable and this is contemplated using deuterium labelling.

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[8] P.L. Corio, Chem.Rev. 60, 363 (1960).

The formation of a cyclic carbonate by the trans-3,4-diol indicates that the production of such derivatives can no longer be regarded as diagnostic for a cis configuration. Doubt has already been cast on the specificity of such tests.[9] The bearing of this work on the configurations assigned on chemical evidence to flavan-3,4-diols synthesized from 3-hydroxyflavan-4-ones will be discussed in another communication.

A very recent note which appeared after this manuscript had been prepared also deals with stereochemistry and NMR spectra of flavan derivatives.[10] We are unable to ascertain whether our assignments are in agreement with this work because the NMR data cited[10] are not related to specific known substances, i.e. compounds are designated only by name and not by definitive and descriptive properties.

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[9] H. Kwart and G.C. Gatos, J.Amer.Chem.Soc. 80, 881 (1958).

[10] J.W. Clark-Lewis and L.M. Jackman, Proc.Chem.Soc. 165 (1961).

Tetrahedron Letters No. 13, pp. 435-439, 1961. Pergamon Press Ltd. Printed in Great Britain.

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THE THERMAL DECOMPOSITION OF α-DIAZOACETOPHENONE

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Department of Chemistry, Harvard University, Cambridge, Mass.

(Received 19 June 1961)

ALTHOUGH the uncatalyzed, thermal decomposition of several α-substituted α-diazoketones has yielded ketenes, these have not been isolated from the decomposition products of α-diazoketones of type $RCOCHN_2$ and investigation of such products has been scant.[3] In connection with a study of the Wolff rearrangement[4] we have examined the thermal decomposition of α-diazoacetophenone in dodecane.

The reaction was carried out in the dark at 140° under nitrogen for 12 hr. The major product (24%), m.p. 288-289° dec., λ_{max}^{KBr} 5.68μ, was identical with the dilactone obtained by Pummerer and Buchta[5] by treatment of 3-benzoyl-2-phenylpropionic acid (I) with dehydrating agents in the presence of air; Wiberg and Hutton[6] have obtained the same product in 9% yield by the irradiation of solid α-diazoacetophenone. The dilactone is now assigned the revised structure (II) on the basis of its infrared spectrum.[6a]

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[1] Present address: Department of Chemistry, University of Toronto.

[2] National Science Foundation Pre-doctoral Fellow, 1956-59.

[3] W.E. Hanford and J.C. Sauer, Org.Reactions III, 108 (1946), and references quoted therein.

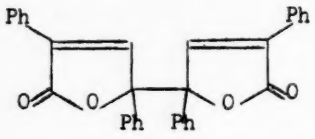
[4] T.J. Clark, Ph.D. Thesis, Harvard (1960).

[5] R. Pummerer and E. Buchta, Ber.Dtsch.Chem.Ges. 69, 1005 (1936).

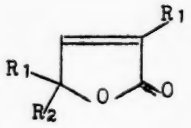
[6] K.B. Wiberg and T.H. Hutton, J.Amer.Chem.Soc. 76, 5367 (1954).

[6a] Professor H.H. Wasserman, Yale University, has kindly informed us that he has reached a similar conclusion regarding the structure of the dilactone: cf. R.M. Waters, Ph.D. Thesis, Yale University (1954); H.H. Wasserman, R.M. Waters, and J.E. McKeon, to be published.

The related monolactone (III) m.p. 107-108°, $\lambda_{max}^{CH_2Cl_2}$ 5.68μ, λ_{max}^{EtOH} 260 mμ (log ε 4.09), was also isolated in 4% yield; it was shown to be identical with the lactone m.p. 108° obtained by Pummerer and Buchta together with compound (II) in their dehydration of compound (I). An authentic sample was prepared by dehydration of compound (I) with acetic anhydride under nitrogen;



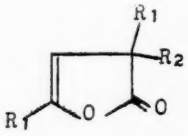
(II)



(III, R_1=Ph, R_2=H)

(V, R_1=Ph, R_2=$C_{12}H_{25}$)

(VIII, R_1=$(CH_3)_3C$, R_2=H)



(IV, R_1=Ph, R_2=H)

(VI, R_1=Ph, R_2=$C_{12}H_{25}$)

(VII, R_1=$(CH_3)_3C$, R_2=H)

(IX, R_1=R_2=Ph)

the crude syrupy product consisted largely of the enol lactone (IV) since its infrared spectrum showed an intense band at 5.55μ with a weaker band at 5.68μ, but the crystalline product, m.p. 107-108° isolated after chromatography on silica, showed a single intense carbonyl band in its infrared spectrum at 5.68μ and therefore must be the isomeric lactone (III).[7]

The following compounds were also isolated from the reaction mixture

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from the decomposition of α-diazoacetophenone and were identified by comparison with authentic samples: benzalacetophenone (8%), acetophenone (3.3%, as its 2,4-dinitrophenylhydrazone), trans-1,2,3-tribenzoylcyclopropane[9] (1.4%), 1,2-dibenzoylethane (0.4%), and benzoic acid (0.1%). In addition, a liquid product (0.7%) was isolated which is considered to be dodecyl phenylacetate since its infrared spectrum very closely resembled that of decyl phenylacetate[4] and it gave phenylacetic acid on hydrolysis. Two further products were isolated, but were obtained in insufficient amount for full purification and characterization: on the basis of their infrared and ultraviolet spectra they are believed to be lactones of type (V) and (VI).

The formation of compound (II) most probably proceeds via oxidation of compound (III), a process known to be facile.[6,10] Since the decomposition reaction was carried out in the absence of air, this oxidation must occur with the concurrent formation of reduction products; such must be the origin of the acetophenone and 1,2-dibenzoylethane. Compound (III) itself is most probably produced via formation of compound (IV); thus, Wiberg and Hutton[6] found that photolysis of 1-diazo-3,3-dimethyl-2-butanone gave, in addition to 2,2,6,6-tetramethyl-4-hepten-3-one,[11] the lactone (VII), which was isomerized to the lactone (VIII) at 180°. These authors suggested that the enol lactone was produced by reaction of the ketene formed by the photolytic decomposition of the diazoketone with unchanged diazoketone. Huisgen,[12] on

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[7] The recent suggestion[8] that the compound, m.p. 288-289°, has structure (IV) is unconvincing; we have found that on hydrolysis it yields both compound (I) and acetophenone, the formation of the latter is readily explicable in terms of structure (II), but not (IV).

[8] W. Davey and D.J. Tivey, J.Chem.Soc. 1230 (1958).

[9] C. Grundmann, Liebigs Ann. 470, 284 (1929); J.F. Neumer, Ph.D. Thesis, Chicago (1957).

[10] Solutions of compound (III) on standing in air slowly deposited compound (II).

[11] Cf. the formation of benzalacetophenone in the thermal decomposition of α-diazoacetophenone.

the other hand, has suggested that the lactone is formed by reaction of the ketene with the species RCOC̈H, postulated as an intermediate in the photochemical conversion of diazoketone to ketene. Because of our interest[4] in establishing whether, in the thermal decompsotion of diazoketones, the formation of ketenes occurs via an intermediate of type RCOC̈H or directly by concerted migration and loss of nitrogen, we have sought to distinguish between these two types of pathway for lactone formation in the case of the thermal decomposition of α-diazoacetophenone.

The rate of decomposition at 139.2° of α-diazoacetophenone in dodecane in the presence of Tenox BHA[13] in evacuated, sealed ampoules was measured by the use of infrared spectrophotometry;[4] the rate was first order in diazoketone with $k = 5.1 \times 10^{-4}$ l.mole^{-1}sec^{-1}. When an excess of diphenylketene was added to the reaction mixtures, the rate was too fast to measure, for over 90% of the diazoacetophenone had reacted in one minute. The product was shown to be the lactone (IX) by its properties, m.p. 120.8-121.4° (lit.[14] m.p. 117-118°), $\lambda_{max}^{CH_2Cl_2}$ 5.55μ, λ_{max}^{EtOH} 270 mμ (log ε 4.18) and its hydrolysis to 3-benzoyl-2,2-diphenylpropionic acid, m.p. 184-185° (lit.[14] m.p. 182-183°), λ_{max}^{KBr} 3-4, 5.86, 5.93μ. The accelerating effect of the addition of diphenylketene on the rate of decomposition of the diazoketone was also witnessed by the fact that, although no decomposition of α-diazoacetophenone in dodecane alone occurs at room temperature, decomposition does occur at room temperature in the presence of diphenylketene. The marked acceleration of the rate of decomposition can be accomodated only in terms of lactone formation by reaction between diazoketone and ketene as

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[12] R. Huisgen, Angew.Chem. 67, 439 (1955).

[13] Tenox BHA (Tennessee Eastman Corporation) is a mixture of 2-t-butyl- and 3-t-butyl-4-methoxyphenol; variation in its concentration has been shown not to affect the rate of decomposition of α-diazoacetophenone.[4]

[14] F.R. Japp and F. Klingemann, J.Chem.Soc. 57, 662 (1890).

proposed for the photolytic reaction by Wiberg and Hutton, and not in terms of a reaction scheme involving reaction of RCOC̈H with ketene. Thus these experiments provide no evidence for the intermediacy of the species RCOC̈H in the thermal conversion of diazoketones to ketenes. They do not, however, exclude this possibility, since rearrangement of such a species to the ketene might well predominate over alternative, intermolecular reactions.

Note: After the submission of this paper, a recent report on the thermal decomposition of α-diazoacetophenone in benzonitrile became available to us: R. Huisgen, H. König, G. Binsch, and H.J. Sturm, Angew. Chem. 73, 368 (1961). A dilactone (19%) and a monolactone (32%) were obtained, which, although formulated as enol lactones, are most probably the compounds II and III, respectively, obtained in the present investigation. In addition, 2,5-diphenyloxazole (0.4%) was isolated; the yield of this product was appreciably increased when copper or copper compounds were used as catalysts. (The formation of 2,5-diphenyloxazole under the latter conditions has been observed in this Laboratory: P. Yates and M.J. Jorgenson, unpublished results.)

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SYNTHESIS OF A TRIMETALLOCENE DERIVATIVE*[1,2]

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(Received 26 June 1961)

THE recently described[3] ferrocenyl ruthenocenyl ketone prompts us to report some of the results we have obtained in the course of an investigation[1] of the chemistry of cyclopentadienylmanganese tricarbonyl (I) and its derivatives.

Compound (I) reacted with (chloroformylcyclopentadienyl)-manganese tricarbonyl (II) under Friedel-Crafts conditions to yield, after the usual work-up and chromatography over alumina, yellow crystals of di-(cyclopentadienylmanganese tricarbonyl)-ketone (III) (28%) m.p. 145-145.5°. (Found: C, 46.84; H, 2.10; Mn, 24.94. $C_{17}H_{10}O_7Mn_2$ requires: C, 46.81; H, 2.31; Mn, 25.19%). The infra-red spectrum of (III) showed the terminal carbonyl absorption at 2030 and 1948 cm^{-1} as well as a ketonic carbonyl absorption at 1647 cm^{-1}. It is interesting to note that the ketonic carbonyl absorption is lower than that of either diferrocenyl ketone[3] (1612 cm^{-1}) or

* Organometallic Studies - IV.

1 Part III: M. Cais and J. Kozikowski, J.Amer.Chem.Soc. 82, 5667 (1960); Part II: A. Modiano and M. Cais, Tetrahedron Letters No. 18 31 (1960); Part I: M. Cais and A. Modiano, Chem. & Ind. 202 (1960).

2 Presented in part at the Meeting of the Israel Chemical Society, Rehovot, 4-5 April, 1961.

3 M. Rausch, E.O. Fischer and H. Grubert, J.Amer.Chem.Soc. 82, 76 (1960).

ferrocenyl ruthenocenyl ketone[3] (1623 cm^{-1}).

The acid chloride (II) (1.33 g) was reacted under similar conditions with ferrocene (0.93 g) and chromatography of the reaction product yielded 1.25 g of scarlet-red crystals, m.p. 148-149° and 0.13 g of purple-red crystals, m.p. 230-232°. The lower m.p. compound turned out to be the expected (cyclopentadienylmanganese tricarbonyl) (1-ferrocenyl)-ketone (IV) (Found: C, 55.15; H, 3.43. $C_{19}H_{13}O_4MnFe$ requires: C, 54.84; H, 3.15%). The infra-red spectrum showed terminal carbonyl absorptions at 2030 and 1940 cm^{-1}, ketonic carbonyl absorption at 1633 cm^{-1} and absorptions at 1003 and 1109 cm^{-1}, indicative of an unsubstituted cyclopentadienyl ring in the ferrocene moiety. The higher m.p. compound showed absorption bands (KBr pellet) at 2030, 1944 and 1929 cm^{-1} assigned to the terminal carbonyl groups, at 1628 cm^{-1} assigned to ketonic carbonyls and no absorption bands near 1000 and 1100 cm^{-1}.

On the basis of the infra-red spectrum and the elementary analysis, this compound was assigned the structure of the diketone V (Found: C, 52.14; H, 2.55; $C_{28}H_{16}O_8FeMn_2$ requires: C, 52.05; H, 2.49%).

This appears to be the first reported derivative in which three metallocene moieties are incorporated into a neutral compound.

The same compound (V) was obtained in 82% yield when the acid chloride (II) was reacted directly with the monoketone (IV), under Friedel-Crafts conditions.

Using the same series of reactions as for (I),[1,4] methylcyclopentadienylmanganese tricarbonyl (VI) was transformed into (x-methyl-y-carboxylcyclopentadienyl)manganese tricarbonyl.

Two isomeric carboxylic acids were separated, one (VIIa) m.p. 180-181°

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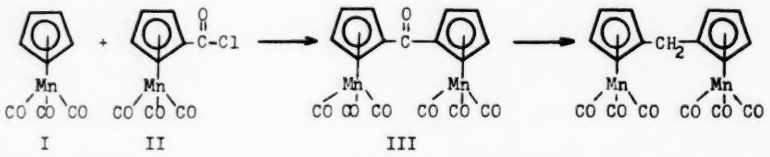
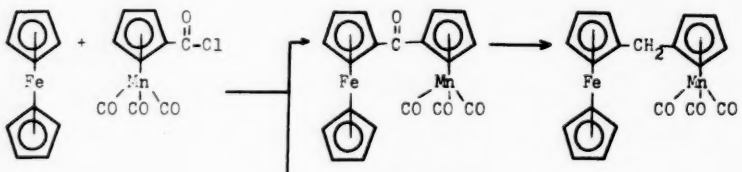
[4] J. Kozokowski and M. Cais, unpublished results.

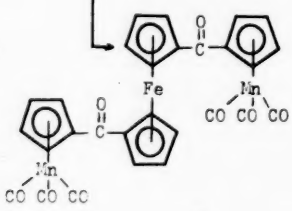
(Found: C, 45.94; H, 2.90; Mn, 21.00. $C_{10}H_7O_5Mn$ requires: C, 45.79; H, 2.69; Mn, 20.96%) and another one (VIIb), m.p. 154-155° (Found: C, 45.93; H, 2.76; Mn, 21.44%). The higher m.p. acid (VIIa) was transformed into the acid chloride (VIII) (with thionyl chloride) and the latter reacted



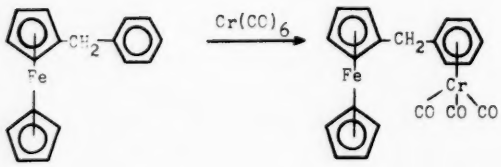
I II III



IV X



V



XI

under Friedel-Crafts conditions with ferrocene to yield over 40% of red crystals (IX). The I.R. spectrum and the elementary analysis of this com-

pound indicated that (IX) was the disubstituted ferrocene derivative analogous to compound (V).

Clemmensen reduction of the ketone (IV) gave the corresponding substituted methane derivative (X), orange crystals, m.p. 121.5-122° (Found: C, 56.80; H, 3.85. $C_{19}H_{15}O_3FeMn$ requires: C, 56.75; H, 3.76%).

The same reduction was carried out with the ketone (III). An analogous compound to (X) was prepared by reacting benzyl ferrocene[5] with chromium hexacarbonyl to yield, among other products, 1-(benzylchromium tricarbonyl)-ferrocene (XI), m.p. 164-165°. (Found: C, 58.52; H, 3.84. $C_{20}H_{16}O_3CrFe$ requires C, 58.28; H, 3.91%).

The infra-red spectrum of (XI) shows the terminal carbonyl absorptions at 1965 and 1893 cm^{-1}, and the unsubstituted-ring absorptions of ferrocene at 1105 and 998 cm^{-1}. A study of the latter reaction as well as an investigation of the reactions of the ketones reported are in progress.

We wish to thank the Israeli Ministry of Commerce and Industry for financial support, Ethyl Corporation, Detroit, Mich., for generous supplies of cyclopentadienylmanganese tricarbonyl and chromium hexacarbonyl, and E.I. DuPont de Nemours and Co., Wilmington, Delaware, U.S.A., for a supply of ferrocene.

---

[5] M. Rausch, M. Vogel and H. Rosenberg, J.Org.Chem. 22, 900 (1957).

Tetrahedron Letters No. 13, pp. 444-447, 1961. Pergamon Press Ltd. Printed in Great Britain.

MIXED π-HYDROCARBONMETAL CARBONYL DERIVATIVES*

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(Received 26 June 1961)

SOME of the research attempts in our laboratory have been directed towards the synthesis of organometallic π-complexes incorporating two or more metallic atoms in the same molecule. In the preceeding communication[1] we have described several such compounds whose synthesis was based on the benzene-like, aromatic properties of the cyclopentadienyl ring in metallocenes.

We now wish to report some results of a different approach to the synthesis of multiple-metal π-complexes of organic molecules.

The displacement of CO groups of metal carbonyls by hydrocarbon ligands has been shown to take place in a variety of cases.[2] The reaction of butadiene with iron pentacarbonyl first described in 1930,[3] has been recently reinvestigated[4] and it has been shown that the resulting compound is the π-complex butadieneiron tricarbonyl.

---

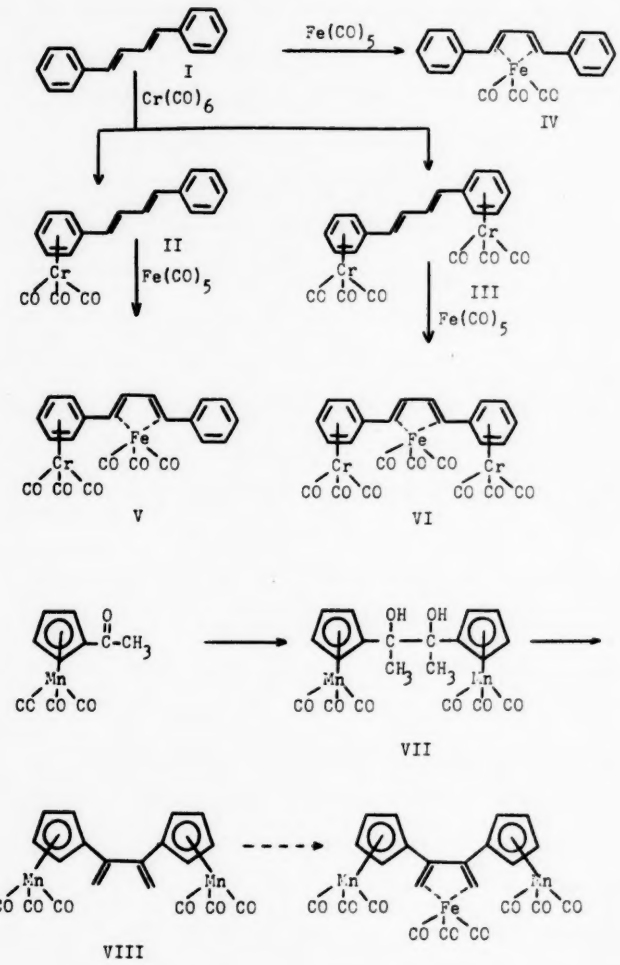
* Organometallic Studies - V.

[1] Part IV: M. Cais and M. Feldkimel, Tetrahedron Letters No. 13, 440 (1961), preceding paper.

[2] For a recent review see Chapters 8 and 10 in H. Zeiss (Editor), Organometallic Chemistry. Reinhold, New York (1960).

[3] H. Reihlen, A. Gruhl, G. Hessling and O. Pfrengle, Liebigs Ann. 482, 161 (1930).

[4] B.F. Hallam and P.L. Pauson, J.Chem.Soc. 642 (1958).



Similarly several authors[5-7] have shown independently that the metal carbonyls react readily with aromatic systems to form arene-carbonylmetal

[5] E.O. Fischer and K. Ofele, Chem.Ber. 90, 2532 (1957).

[6] G. Natta, R. Ercoli and F. Calderazzo, Chim. e Ind. 40, 287 (1958).

[7] M.C. Whiting and B. Nicholls, J.Chem.Soc. 551 (1959).

complexes.

We have combined the above two reactions to obtain novel compounds of the type described below. For example, when 1,4-diphenylbutadiene (I) was reacted with chromium hexacarbonyl, we isolated two compounds: 1-(phenylchromium tricarbonyl)-4-phenylbutadiene (II) (60% yield), orange-red crystals, m.p. 150-152° (Found: C, 66.69; H, 4.22; Cr, 16.00. $C_{19}H_{14}CrO_3$ requires: C, 66.66; H, 4.12; Cr, 15.2%); and a small amount of 1,4-di-(phenylchromium tricarbonyl)butadiene (III), red crystals, m.p. 174-176° (Found: C, 55.51; H, 2.85; Cr, 21.80. $C_{22}H_{14}Cr_2O_6$ requires: C, 55.24; H, 2.95; Cr, 21.75%). Compound (III) was obtained in over 50% yield when (II) was reacted again with chromium hexacarbonyl. All three compounds, (I), (II) and (III) were then reacted with iron pentacarbonyl to give respectively 1,4-diphenylbutadieneiron tricarbonyl (IV), yellow orange crystals, m.p. 165-166° (Found: C, 65.82; H, 4.10. $C_{19}H_{14}O_3Fe$ requires: C, 65.92; H, 4.07%); 1-(phenylchromium tricarbonyl)-4-phenyl-butadieneiron tricarbonyl (V) m.p. 186-188° (dec.) (Found: C, 55.04; H, 2.98. $C_{22}H_{14}O_6CrFe$ requires: C, 54.80; H, 2.92%) and 1,4-di(phenylchromium tricarbonyl)butadieneiron tricarbonyl (VI), m.p. 191-193° (dec.)(Found: C, 48.36; H, 2.27. $C_{25}H_{14}O_9Cr_2Fe$ requires: C, 48.57; H, 2.28%).

The same series of reactions was carried out with 1-phenylbutadiene and work is currently in progress to extend these reactions to other systems containing both arene and conjugated diene moieties in the same molecule.

As an example of such an extension we wish to mention the preparation of the pinacol (VII), yellow crystals, m.p. 163-165° (Found: C, 48.82; H, 3.14; Mn, 22.24. $C_{20}H_{14}H_8Mn_2$ requires: C, 48.56; H, 3.26; Mn, 22.23) and its dehydration to the substituted butadiene (VIII), yellow crystals, m.p. 116-117° (Found: C, 52.69; H, 2.75; Mn, 24.22. $C_{20}H_{12}O_6Mn_2$ requires C, 52.43; H, 2.64; Mn, 23.98%). The reaction of VIII with iron pentacarbonyl

is under investigation.

The infra-red spectra and ultra-violet spectra of the new compounds have been measured and details will be published in the full paper.

We wish to thank the Israeli Ministry of Commerce and Industry for financial support and Ethyl Corporation, Detroit, Mich., U.S.A., for generous samples of metal carbonyls.

Tetrahedron Letters No. 13, pp. 448-451, 1961. Pergamon Press Ltd. Printed in Great Britain.

1961

CORTICOSTEROID 17α-MONOESTERS FROM 17α,21-CYCLIC ORTHOESTERS

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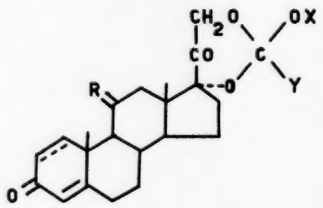
(Received 19 June 1961; in revised form 17 July 1961)

IN pursuing our work concerned with the preparation, by an interchange reaction, of 17α,21-cyclic derivatives of corticosteroids with dihydroxy acetone side chain,[1] we have prepared a great number of 17α,21-orthoesters of corticosteroids, including cortisone, cortisol, cortexolone and their 1-dehydro derivatives.[2]

These compounds were obtained from the 17α,21-diol and a lower alkyl orthoester by brief distillation in benzene in the presence of a small



R = H_2, = O, = **; X = lower alkyl; Y = H or alkyl**

[1] R. Gardi, R. Vitali and A. Ercoli, In press; see also M. Tanabe and B. Bigley, J.Amer.Chem.Soc. 83, 756 (1961).

[2] 16α,17α-Cyclic orthoesters of triamcinolone have been prepared recentl by L.L. Smith and M. Marx, J.Amer.Chem.Soc. 82, 4625 (1960).

amount of an acid catalyst;[3] the yields varied between 45 and 80%.

Two isomers are possible owing to the new asymmetric carbon atom. At least in the case of orthoformates, we have been able not only to isolate the two epimers, but also to obtain their stereospecific synthesis by a proper choice of the acid catalyst. Thus, as briefly exemplified in the table, the use of pyridine hydrochloride leads to the formation of the more dextro rotatory epimer, whereas a reaction catalysed by p-toluenesulphonic acid furnishes the epimer with negative M_D contribution.

Compound	Catalyst	M.p.	$[\alpha]_D$	ΔM_D (M_D orthoester-M_D parent diol)
R = O; Y = H; X = C_2H_5	Py.HCl	164-166°	+198°	+111
	TsOH	187-189°	+162°	- 39
R = O; Y = H; X = C_2H_5; Δ^1	Py.HCl	157-159°	+184°	+146
	TsOH	210-211°	+140°	- 35
R = ;Y=H; X = C_2H_5; Δ^1	Py.HCl	140-142°	+126°	+157
	TsOH	198-200°	+ 85°	- 13

The 17α,21-orthoesters are quite stable to base, remaining unchanged after refluxing for 2 hr in methanolic N KOH; they are hydrolysed in various manners by acids. Thus, by heating for 10 min in methanol with a few drops of N HCl, the cyclic orthoformates regenerate the starting free alcohols in high yield. By carrying out the hydrolysis with HCl at room temperature or with oxalic acid by heating, a mixture of 17α-monoformate and 21-monoformate is obtained, which can be resolved by fractionated crystallization. For instance, we have thus prepared prednisolone 17α-monoformate, m.p. 244-245°, $[\alpha]_D$ +20°.[4]

[3] By this procedure we did not observe formation of 3-enol ethers.

[4] Melting points uncorrected, rotations in dioxane. Satisfactory analyses have been obtained for all compounds mentioned.

By a similar procedure prednisolone 17α,21-methylorthoacetate, m.p. 214-216°, $[\alpha]_D$ +61°, furnishes, as a major product, the 17α-monoacetate, m.p. 240-242°, $[\alpha]_D$ +10°, in addition to small amounts of 21-ester. Accordingly, cortisol 17α-monoacetate, m.p. 234-237°, $[\alpha]_D$ +50°, was easily prepared.

Prednisone 17α-monovalerate, m.p. 198-201°, $[\alpha]_D$ +69°, is virtually the sole product of the hydrolysis of prednisone 17α,21-methylorthovalerate, m.p. 200-203°, $[\alpha]_D$ +114°, even if carried out with HCl by heating. Similarly, prednisolone 17-monovalerate, m.p. 210-213°, $[\alpha]_D$ +3,5°, was quantitatively obtained.

The structure of these esters was assigned on the basis of elemental analyses, papergram mobilities and infrared spectra, and also confirmed by acylation to 17α,21-diesters, identical with the products prepared, when possible, by a different route.[5]

Up to now, the 21-oxygenated 17-monoesters have been inaccessible, since one can not selectively acylate the 17α-hydroxyl in the presence of 21-oxygen and means are not known for selectively hydrolysing at 21 in a 17α,21-diester.[6]

A tentative explanation for the formation of the 21-monoester beside the 17α-monoester after the hydrolysis of 17α,21-orthoesters might be found in another unexpected finding: by refluxing in benzene in the presence of p-toluenesulphonic acid, corticosteroid 17α-monoesters readily rearrange to the corresponding 21-monoesters in quantitative yield. The isomerization rate decreases, as a rule, by increasing the acylic chain length. Therefore we could assume that hydrolysis of 17α,21-orthoesters affords, at first, the 17α-monoester only, which can partially rearrange to the 21-monoester.

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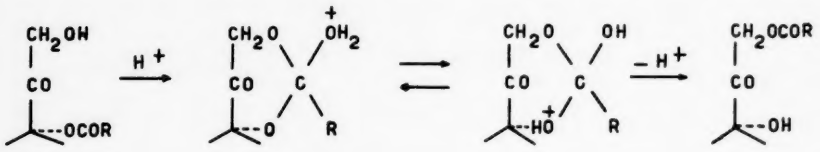
[5] R.B. Turner, J.Amer.Chem.Soc. 75, 3489 (1953).

[6] Cf. H.J. Ringold, G. Rosenkranz and F. Sondheimer, J.Amer.Chem.Soc. 78, 820 (1956).

Seemingly, hydrolysis of 17α, 21-orthoesters to 17α-monoesters occurs with the initial split of the C-O-C bond at C-21.[7] This is also indirectly supported by the assumption of a mechanism via an ortho form for the rearrangement of the 17α-monoester, as reported for other acyl migrations.[8]



This rearrangement might also account for the impossibility to hydrolyse selectively a 17α,21-diester, since conditions for hydrolysis could effect the acyl migration. Others have postulated this kind of rearrangement in basic medium and proposed a cyclic orthoester as an intermediate.[6,9]

According to our previous findings on acetal formation,[1] we have also obtained, as a side-product of the interchange reaction between prednisolone and ethyl orthoformate, a bis-orthoester, the 11-diethoxymethyl ether of 17α, 21-ethylorthoformate, m.p. 144-146°, $[\alpha]_D$ +116°. Its hydrolysis afforded prednisolone 11-monoformate, m.p. 225-228°, $[\alpha]_D$ +127°.

Studies on further acid-catalysed transformation products of steroidal 17α,21-orthoesters are in progress.

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[7] Cf. S. Winstein and B.E. Buckles, J.Amer.Chem.Soc. 65, 613 (1943).

[8] H. Gillman, Organic Chemistry Vol. II, pp. 1610-1611. John Wiley, New York (1947).

[9] L.F. Fieser and M. Fieser, Steroids p. 680. Reinhold, New York (1959).

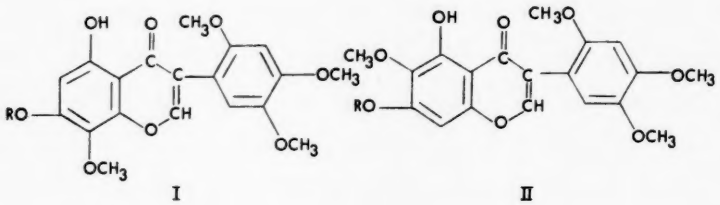
Tetrahedron Letters No. 13, p. 452, 1961. Pergamon Press Ltd. Printed in Great Britain.

ERRATA

LORÁND FARKAS und JÓZSEF VARÁDY: Synthese des Caviunins, Tetrahedron Letters No. 6, 197 (1961).

The authors have requested the following amendments to the above article:

(a) formulae I and II on p. 197 should read:



(b) the eighth and ninth lines of p. 197 should read:

..... 5-Hydroxy-6,2',4',5'-tetramethoxy-7 benzyloxy-isoflavon .....

Tetrahedron Letters No. 14, pp. 453-454, 1961. Pergamon Press Ltd. Printed in Great Britain.

DERIVATION OF GENTIANIN FROM SWERTIAMARIN

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(Received 9 June 1961; in revised form 24 July 1961)

SWERTIA japonica Makino was found to contain, besides swertiamarin (Ia or Ib),[1] an alkaloid gentianin,[2] the biogenesis of which was recently discussed by Govindachari, Nagarajan and Rajappa [3], and Wenkert and Bringi[4] respectively.

This paper describes the derivation of gentianin from swertiamarin under mild conditions.

Swertiamarin acetate (Ic or Id), $C_{24}H_{30}O_{14}$, m.p. 190-191° (300 mg) was dissolved in methanol (20 cc), concentrated aqueous ammonia (20 cc) was added and the solution allowed to stand until the bitterness was lost. Three days later, the solvent was removed under reduced pressure, and 5% hydrochloride acid was added to the amorphous residue, which shows properties of a glucoside, and the solution was refluxed for 30 min. After cooling, the neutral and acidic parts were removed with ether, the acidic solution made alkaline with ammonia and extracted with chloroform. The extract washed with water, dried and evaporated to dryness gave a pale yellow crystalline residue. Recrystall-

[1] T. Kubota and Y. Tomita, Tetrahedron Letters No. 5, 176 (1961).

[2] S. Shibata, M. Fujita and H. Igeta, J.Pharm.Soc.Japan 77, 116 (1957).

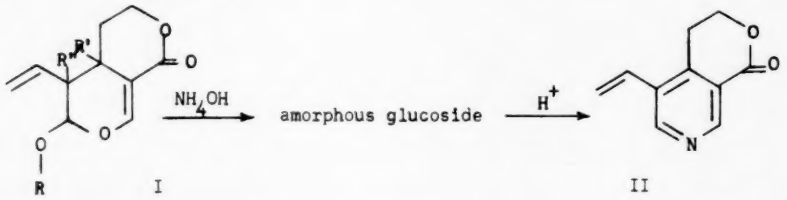
[3] T.R. Govindachari, K. Nagarajan and S. Rajappa, Experientia 14, 5 (1958).

[4] E. Wenkert, and N.V. Bringi, J.Amer.Chem.Soc. 81, 1474 (1959).

ization from petroleum ether gave colourless long needles, m.p. 82-83° (38 mg).

By mixed melting point and comparison of the infra-red absorption spectrum, this substance was found to be identical with gentianin (II), m.p. 82-84°, isolated from Swertia japonica Makino.

Therefore, the carbon skeleton of the formula I for swertiamarin may be positively established although the position of the tertiary hydroxyl group remains to be established.



I II

Ia; R=Glucose, R'=OH, R"=H
Ib: R=Glucose, R'=H, R"=OH
Ic: R=Glu(Ac)4, R'=OH, R"=H
Id: R=Glu(Ac)4, R'=H, R"=OH

Since the reaction described above proceeds under mild conditions, it is possible that gentianin can be produced in substantially the same manner in the plant.

Tetrahedron Letters No. 14, pp. 455-457, 1961. Pergamon Press Ltd. Printed in Great Britain.

C-ACYLIERUNG VON TRIPHENYLPHOSPHIN-ALKYLENEN MIT AKTIVIERTEN ESTERN

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Organisch Chemisches Institut der Technischen Hochschule, München

(Received 20 July 1961)

TRIPHENYLPHOSPHIN-ALKYLENE lassen sich mit Säurechloriden nach folgendem Schema acylieren:[1]

$$2\ R\text{-}CH{=}P(C_6H_5)_3 + R'\text{-}CO\text{-}Cl \longrightarrow R\text{-}\underset{\underset{P(C_6H_5)_3}{\|}}{C}\text{-}CO\text{-}R' + [R\text{-}CH_2\text{-}\overset{\oplus}{P}(C_6H_5)_3]Cl^{\ominus}$$

Wir haben nun gefunden, dass man statt der Säurechloride auch aktivierte Ester verwenden kann, wie z.B. Phenylester oder Thiophenylester. Dabei entstehen neben den Triphenylphosphin-acyl-alkylenen die entsprechenden Phosphonium-phenolate bzw. Thiophenolate.

Die Reaktion mit diesen Verbindungen verläuft in zwei Stufen:

$$(1)\quad \underset{\text{I}}{2\ R\text{-}CH{=}P(C_6H_5)_3} + \underset{\text{II}}{R'\text{-}CO\text{-}SC_2H_5} \longrightarrow \underset{\text{III}}{R'\text{-}CO\text{-}\underset{\underset{P(C_6H_5)_3}{\|}}{C}\text{-}R} + \underset{\text{IV}}{[R\text{-}CH_2\text{-}\overset{\oplus}{P}(C_6H_5)_3]\overset{\ominus}{S}C_2H_5}$$

$$(2)\quad \underset{\text{IV}}{[\,R\text{-}CH_2\text{-}\overset{\oplus}{P}(C_6H_5)_3]\overset{\ominus}{S}C_2H_5} \rightleftharpoons \underset{\text{I}}{R\text{-}CH{=}P(C_6H_5)_3} + HSC_2H_5$$

Das zunächst gebildete Phosphonium-äthylmercaptid IV spaltet in einer Gleichgewichtsreaktion beim Erwärmen Mercaptan ab. Dabei entsteht das Ylid I, das mit weiterem Thiolester reagiert und so aus dem Gleichgewicht entfernt

[1] H.J. Bestmann, Tetrahedron Letters No. 4, 7 (1960).

wird. Es resultiert also folgender Gesamtreaktionsablauf:

$$R\text{-}CH{=}P(C_6H_5)_3 + R'\text{-}CO\text{-}SC_2H_5 \longrightarrow R'\text{-}CO\text{-}\underset{\underset{P(C_6H_5)_3}{\|}}{C}\text{-}R + HSC_2H_5$$

Man spart also gegenüber dem Säurechloridverfahren 1 Mol Phosphinalkylen ein.

Zum Beweis des Vorliegens des in Gleichung 2 angeführten Gleichgewichtes wurde aus Triphenylphosphin-methylen und Aethylmercaptan das kristallisierte Phosphoniummercaptid (IV,R=H) dargestellt, und dieses dann unter Erwärmen mit Benzophenon umgesetzt. Dabei entsteht durch Wittig-Reaktion mit dem im Gleichgewicht befindlichen Triphenylphosphin-methylen (I,R=H) 1,1-Diphenyl-äthylen neben Aethylmercaptan.

In der folgenden Tabelle sind die durch Acylierung von Triphenylphosphin-alkylenen mit Thiolestern dargestellten Triphenylphosphin-acyl-alkylene aufgeführt.

Triphenylphosphin-acyl-alkylene $R\text{-}\underset{\underset{P(C_6H_5)_3}{\|}}{C}\text{-}CO\text{-}R'$

Nr	R	R'	Schmp (°C)	Ausbeute in % d. Th bez. auf einges. Thiolester
1	H	CH_3	200	78
2	H	C_6H_5	180	80
3	H	$C_6H_5\text{-}CH_2\text{-}CH_2$	149	80
4	CH_3	C_6H_5	170	93
5	CH_3	$C_6H_5\text{-}CH{=}CH$	205	68
6	CH_3	$C_6H_5\text{-}CH_2\text{-}CH_2$	165	76

Aus den Verbindungen 1-6 lassen sich durch Wittig-Reaktion,[1,2] durch

[2] G. Wittig und U. Schöllkopf Chem.Ber. 87, 1318 (1954); F. Ramirez und S. Dershowitz J.Org.Chem. 22, 41 (1957).

Hydrolyse[1] oder durch reduktive Spaltung mit Zink in Eisessig[3] verschiedenartigste Ketone gewinnen.

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[3] vergl. S. Trippett und D.M. Walker, J.Chem.Soc. 1266 (1961).

Tetrahedron Letters No. 14, pp. 458-460, 1961. Pergamon Press Ltd. Printed in Great Britain.

THE PYRIDINE CATALYSED HYDROLYSIS OF CARBOXYLIC ANHYDRIDES

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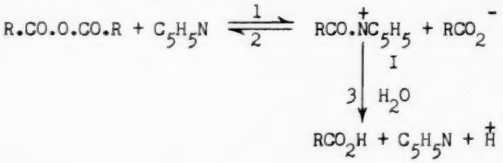
(Received 6 July 1961)

TERTIARY amines, e.g. pyridine, are effective catalysts of the hydrolysis of carboxylic anhydrides. Pyridine is believed to act by converting the anhydride into an acylpyridinium ion (I). Both the formation of this ion, step 1, and its breakdown to products, step 3, have at times been postulated as the slow step of the reaction.[1a,b]



We have attempted to differentiate between these possibilities by studying the concurrent hydrolysis and isotopic exchange of anhydrides with ^{14}C-labelled carboxylate.

In the absence of pyridine, hydrolysis of acetic anhydride in the presence of sodium acetate is accompanied by isotopic exchange between the

[1a] V. Gold and E.G. Jefferson, J.Chem.Soc. 1409 (1953); [b] A.R. Butler and V. Gold, Proc.Chem.Soc. 15 (1960).

TABLE 1

Rates of Acetate Exchange and Hydrolysis of Acetic Anhydride in Water at 0°

$[Ac_2O] = 0.3M$

[Pyridine] mM	$[\bar{O}Ac]$ M	10^3 rate Hydrolysis*	mole l^{-1} sec^{-1} Exchange
0	0.5	0.21	ca. 0.9
0	1.0	0.29	1.3
4	0.5	0.69	13.5
4	1.0	0.74	12.7

*Calculated from experiments with $[Ac_2O]$ $^M/_{20}$

anhydride and the acetate ion (Table 1).

$$R.CO.O.\dot{C}O.R + R\overset{14}{C}O_2^- \rightleftharpoons R.\overset{14}{C}.O.O.CO.R + RCO_2^-$$

Addition of pyridine accelerates both exchange and hydrolysis (Table 1), and from the extents of these rate increase we can calculate the number of acetylpyridinium ions I which revert to reactants, with isotopic exchange, (step 2) relative to those which go forward to products of hydrolysis (step 3). With both 0.5 M and 1 M sodium acetate the rate of step (2) is ca. 25 times that of step (3), and hence in these conditions we can regard I as being in equilibrium with the reactants. The relative rates of steps (2) and (3) are apparently unaffected by a doubling of the concentration of acetate ion, and because the rate of step (2) should depend upon the concentration of acetate ions we conclude that the rate of step (3), the hydrolysis of I, must also be acetate dependent. Qualitatively similar results are observed for the pyridine catalysed exchange of sodium benzoate with benzoic anhydride in aqueous dioxan; where with 0.4 M sodium benzoate + 0.4 M benzoic acid and 0.05 M pyridine the back reaction was ca. 40 times as fast as the forward.

The large solvent deuterium isotope effect on the pyridine catalysed

hydrolysis of acetic anhydride,[1b] can be explained in terms of hydrogen bonding interactions between the solvent and the reactants and transition state,[2] provided that we assume that the transition state for the overall reaction is that for step (3), the attack of water upon I.

[2] C.A. Bunton and V.J. Shiner, J.Amer.Chem.Soc. 83, 42 (1961), and forthcoming publications.

Tetrahedron Letters No. 14, pp. 461-467, 1961. Pergamon Press Ltd. Printed in Great Britain.

MOLECULAR ROTATION AND ABSOLUTE CONFIGURATION - III[1]

EPIMERIC KETONES

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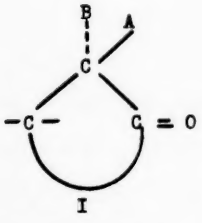
(Received 14 July 1961)

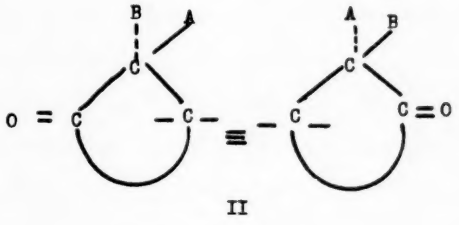
AN EMPIRICAL rule correlating molecular rotation with the absolute configuration of epimeric cyclic compounds was described earlier.[1,2] For the special case where the epimers have a keto group adjacent to the asymmetric center under consideration, the rule may be stated as follows:

In the epimeric ketones I and II, if B be the bulkier of the two exocyclic substituents A and B, I should be more dextrorotatory than II.[3]



I

more dextro



II

more levo

This rule was used to predict that the absolute configuration at C_{11}

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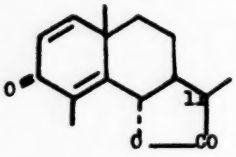
[1] Part II: A.K. Bose and B.G. Chatterjee, J.Org.Chem. 23, 1425 (1958).

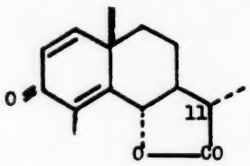
[2] A.K. Bose, Abstracts of XVIth International Congress of Pure and Applied Chemistry, Paris, 1957, p. 141.

[3] For the more generalized rule and a mnemonic, see ref. 1.

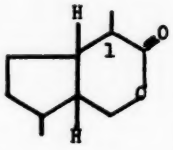
in (-)-santonin and (-)-β-santonin should be as shown in III and IV respectively.[2] The recent work of Barton and Pinhey[4] leaves little doubt that III does indeed represent the absolute configuration of (-)-santonin. From the $[\alpha]_D$ values of the lactones iridomyrmecin and isoiridomyrmecin which are epimeric at C_1 we predicted[5] that the absolute configuration of isoiridomyrmecin should be as shown in V. X-ray crystallography[6] of isoiridomyrmecin (iridolactone) has also led to the same stereoformula V.



III



IV



V

Dauben et al.[7] applied this rotation rule to γ-santonin derivatives which are epimeric at C_{11} and deduced absolute configurations which appear to be correct in the light of the subsequent work of Barton and Pinhey.[4]

To test our more general rule[1] we have scanned a very extensive compilation[8] on steroids and found only a few epimeric pairs that do not conform to the rule. The comments in the present communication, however, will be

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[4] D.H.R. Barton and J.T. Pinhey, Proc.Chem.Soc. 279 (1960).

[5] Presented before the "Meeting-in-Miniature", January 1960 of the North Jersey Section of the American Chemical Society.

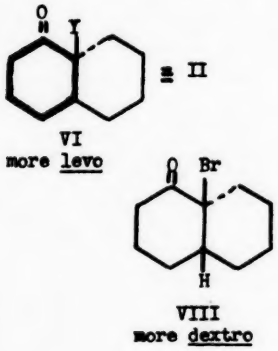
[6] J.F. McConnell and B.P. Schoenborn, Abstracts of the International Congress of Pure and Applied Chemistry Symposium on the Chemistry of Natural Products, Australia, August 1960, p. 44.

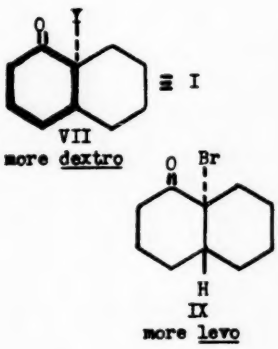
[7] W.G. Dauben, W.K. Hayes, J.S.P. Schwarz and J.W. McFarland, J.Amer. Chem.Soc. 82, 2232 (1960).

[8] J.P. Mathieu and A. Petit, Constantes Selectionees Pouvoir Rotatoire Naturel I. Steroides. Masson et Cie, Paris (1956).

restricted to only those epimeric steroids that have a keto group adjacent to the epimeric center.

Of special interest are derivatives of 1-ketodecalones which are epimeric around the ring junction C_9 (such as VI and VII). For the purposes of our rule, VI and VII are considered to be derivatives of the ring bearing the keto group; the other ring and the angular substituent are counted as the two exocyclic substituents on this ring. It then follows from our rule that in general VI should be more levorotatory than VII. This relationship will be reversed, however, if Y has to be considered the "bulkier" of the two exocyclic substituents. One such example is the case when Y is bromine as in the epimeric pair VIII and IX (see Table 1). The stereochemistry of the few epimers that do not conform to the rule is being investigated.





Recently epimeric α-haloketones have attracted considerable attention. The empirical axial α-haloketone rule[9] and the more comprehensive Octant rule[10] have been used to deduce the absolute configuration of α-haloketones

[9] C. Djerassi, Optical Rotatory Dispersion p. 120. McGraw-Hill, New York (1960).

[10] Ref. 9, p. 178.

Table 1

Prediction from rule:	more levo isomer			more dextro isomer			Ref.
Compound	$[\alpha]_D$	Cotton effect extremum		Epimer	$[\alpha]_D$	Cotton effect extremum	
		mμ	$[\alpha]$			mμ $[\alpha]$	
2α-Bromo-2β-methylcholestan-3-one, ring A: boat	-30°	340	-1180°	2β-Bromo-2α-methyl-, ring A: chair	+140°	335 +2920°	11
2α-Bromo-2β-methylandrostan-17β-ol-3-one acetate, ring A: boat	-6°	338	-494°	2β-Bromo-2α-methyl-, ring A: chair	+100°	330 +2480°	12
(-)-2α-Bromo-cis-1-decalone	-175°	335	-2650°	(-)-2β-bromo-	-55°	319 -234°	13
(-)-9β-Bromo-trans-1-decalone (IX)	-150°	328	-2900°	9-epimer (VIII)	+50°	332 +3100°	13
16α-Bromoisoandrosterone acetate	+56°	342	+1290°	16β-Bromo-	+112°	342 +2097°	14
3-exo-Chlorocamphor	+35°	330	1810°	3-endo-Chloro-	+95°	331 +1798°	14
16α-Bromo-3β-acetoxy-5α, 14-β-androstan-17-one	+58	312	+942°	16β-Bromo-	+104°	342 +1195°	15

Table 2

	I.R. ($CHCl_3$) cm^{-1}	$\Delta\nu$	U.V. (MeOH) λmax (mμ)	$\Delta\lambda$	R.D. trough mμ	$[\alpha]$	R.D. peak mμ	$[\alpha]$
3β-Methoxyandrostan-16-one	1736		296		319	-2860°	269	+2900° (MeOH)
					322	-2550°	277	+2560° (CCl_4)
17β-bromo-	1754	+18	297	+1	319	-3440°	272	+2810° (MeOH)
					327	-2240°	280	+2480° (CCl_4)
17α-bromo-	1748	+12	316	+20	345	-388°	308	+327° (MeOH)
					345	-276°	322	+260° (CCl_4)

11 C. Djerassi, N. Finch, R.C. Cookson and C.W. Bird, J.Amer.Chem.Soc. 82, 5488 (1960).

12 R. Mauli, H.J. Ringold and C. Djerassi, J.Amer.Chem.Soc. 82, 5494 (1960).

13 C. Djerassi and J. Staunton, J.Amer.Chem.Soc. 83, 736 (1961).

14 C. Djerassi, J. Osiecki, R. Riniker and B. Riniker, J.Amer.Chem.Soc. 80, 1216 (1958).

15 J. Fishman and T. Nambara, Chem. & Ind. 79 (1961).

from their optical rotatory dispersion. Before these rules can be applied, it is necessary to determine whether the halogen is in the axial or equatorial position and whether the ring is in the chair or boat conformation. In contrast, our rule appears to be applicable to the $[\alpha]_D$ values of epimeric α-haloketones without regard to the conformation of substituents or the shape of the ring. In Table 1 we report the application of our rule to a few representative epimeric ketones for which the optical rotatory data also are available. It may be noted that the rule allows the correct prediction of the absolute configuration even when one of the epimeric pair is in the chair form and the other in the boat form. Furthermore, the predictions from this rule are valid for the comparison of the $[\alpha]_D$ values of the epimers as well as for the comparison of their Cotton effect curves. The rule therefore assumes added usefulness when both epimers give Cotton effect curves of the same sign.

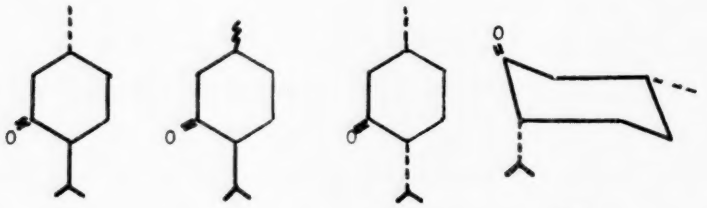
For some epimeric cyclopentanone derivatives the application of the haloketone rule or the Octant rule might be precluded because of the difficulty in ascertaining the conformation of a substituent from spectroscopic data. As examples one can cite the epimeric 16-bromoisoandrosterone acetates and 3-chlorocamphors (see Table 1). The application of our rule leads to the correct stereochemistry in both of these cases as well as in the case of the epimeric 16-bromo-3β-acetoxy-5α, 14β-androstane-17-ones,[15] (see Table 1).

We have determined the spectra for epimeric 17-bromo-3β-methoxyandrostane-16-ones (see Table 2). Predictions from our rule, as well as from the axial α-haloketone rule, are in agreement with the stereochemistry assigned to these isomers by Fajkoš.[16]

[16] Private communication.

Our empirical rule is similar to Brewster's Conformational Dissymmetry Rule[17,18] in some respects but not exactly equivalent to it. While the Octant Rule and Brewster's Rule permit predictions about the rotation of an individual epimer, our rule is more limited since it is explicitly stated in terms of the difference in rotation of an epimeric pair. There is an important advantage in comparing the $[\alpha]_D$ of two epimers (in the same solvent) because in general the effects of the distant environment on the keto group assume secondary importance at long wave lengths. Such a comparison therefore reveals the effect of the immediate environment of the keto group. This may account for the fact that our rule can lead to correct predictions of the configuration of epimers without taking into account their conformation.

The difference in approach of these three rules can be illustrated by considering the ORD of (-)-menthone (X) and its epimer (+)-isomemthone (XI). The former gives a weak positive Cotton effect curve that starts on the negative side in the visible spectral range, while (+)-isomenthone is



X Xa XI XIa

characterized by a strongly positive Cotton effect curve.[19] The Conformational Dissymmetry Rule leads to the prediction that XI in all chair forms should have a positive Cotton effect (not necessarily near 300 mμ) whereas

[17] J.H. Brewster, J.Amer.Chem.Soc. 81, 5475, 5483, 5493 (1959).

[18] J.H. Brewster, Tetrahedron 13, 106 (1961).

[19] Reference 9, p. 105.

the Octant Rule will permit a positive Cotton effect if isomenthone has the conformation XIa in which the bulky isopropyl group is in the axial position. In applying our rule we disregard the conformation and correctly predict that the more levo-rotatory of the two epimers (i.e. (-)-menthone, notwithstanding its positive Cotton effect curve) should have the absolute configuration Xa.

We are grateful to Dr. J. Fajkoš for samples of epimeric 17-bromo-16-ketones. Thanks are due to Dr. M.S. Manhas for assistance in determining the spectra and to Dr. L. Jampolsky and Dr. L.Z. Pollara for valuable suggestions. We also thank Dr. J.H. Brewster for sending us his manuscripts before publication, and for his helpful comments on our manuscript. This work was supported in part by a research grant from the National Science Foundation (NSF - G13290).

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1961

THE DETERMINATION OF π-ELECTRON DENSITIES IN AZULENE FROM C^{13} AND H^1 NUCLEAR RESONANCE SHIFTS*

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(Received 2 June 1961; in revised form 29 June 1961)

THERE is a considerable amount of evidence, derived mainly from measurements on substituted benzenes, to suggest that C^{13} and H^1 chemical shifts are related to the local π-electron density in aromatic molecules. In order to investigate the quantitative relationship between chemical shift and electron density we have measured the C^{13} resonance shifts of the series $C_5H_5^-$, C_6H_6, $C_7H_7^+$ and $C_8H_8^{2-}$, in each of which the local π-electron density is known. The H^1 resonances of the first three members of this series have been measured by Leto, Cotton and Waugh[1], and by Fraenkel, Carter, McLachlan and Richards.[2] Fig. 1 shows the relative C^{13} chemical shifts plotted against the π-electron density, ρ. The corresponding H^1 chemical shifts reported in ref. 2 above are also shown. In magnitude the C^{13} shifts are some fifteen times larger than the corresponding H^1 shifts. The striking parallelism of the resonance shifts of the two nuclei, which has also been observed in the resonance shifts of monosubstituted benzenes,[3] implies that the resonances of both

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* Issued as N.R.C. No. 6345.

[1] J.R. Leto, F.A. Cotton and J.S. Waugh, Nature,Lond. 180, 978 (1957).

[2] G. Fraenkel, R.E. Carter, A. McLachlan and J.H. Richards, J.Amer.Chem. Soc. 82, 5846 (1960).

[3] H. Spiesecke and W.G. Schneider, J.Chem.Phys. In press (1961).

nuclei respond in a parallel way to the local π-electron density on the carbon atom.

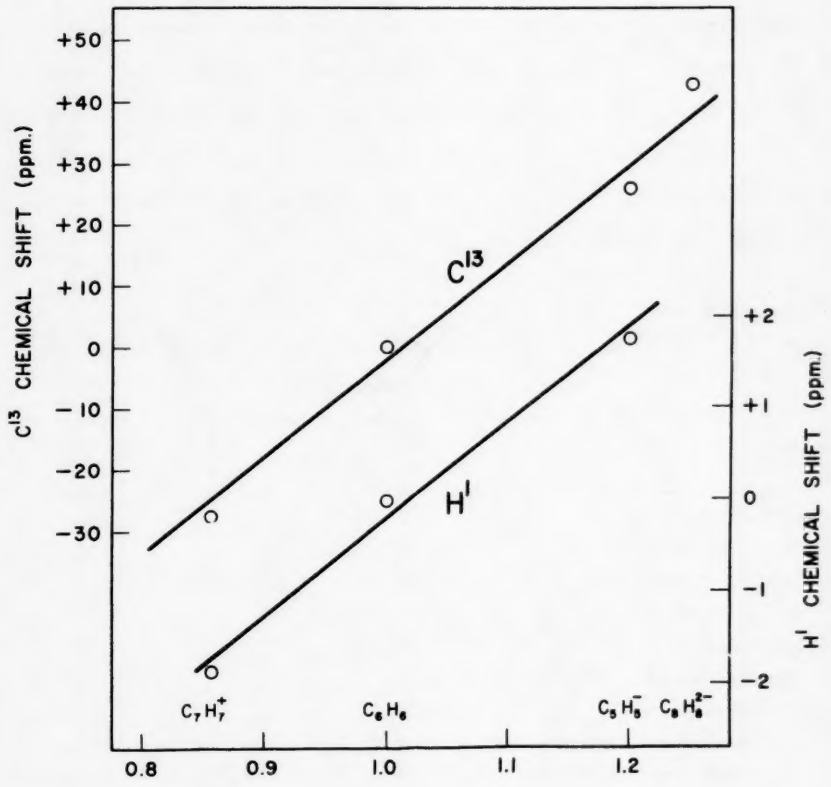

FIG. 1.

The slope of the averaged lines in Fig. 1 yields the proportionality factors, $\delta_{C}13 = 160\rho$ and $\delta_{H}1 = 10.6\rho$.* In both cases, however, the deviation of the individual points from the linear correlation line exceeds

* A value of 160 p.p.m. per electron has also been deduced from C^{13} shifts by Lauterbur (private communication) by an indirect procedure.

the experimental error of the δ-measurements. A satisfactory explanation of these deviations is not immediately apparent. The bond angle varies slightly in the different ring systems and the consequent changes in bond hybridization of the carbon orbitals may be expected to contribute to the resonance shifts. However, examination of the C^{13} shifts of the corresponding cyclic olefins (Table 1) reveals no discernable trend with ring size, nor is there any consistent pattern in the magnitudes of the C-H spin-coupling constants. The latter have been shown to reflect changes in bond hybridization in other compounds.[4,5]

Table 1

Relative C^{13} Chemical Shifts of CH Groups in Olefinic and Aromatic Compounds

Compound	$\delta_{C^{13}}$ (p.p.m. relative to benzene)	J_{CH} (C/S)
Cyclooctatetraene	-4.1	155
Cycloheptatriene	-2.9,1.3,7.6	156,154,161
1,3-Cyclohexadiene[a]	2.4	163
Cyclopentadiene[b]	-4.2	170
Butadiene[c]	-9.5	158
Cyclooctatetraene dianion	42.5	145
Tropylium ion	-27.6	171
Cyclopentadienyl anion	25.7	157

[a] Two broad doublets unresolved

[b] No resolved shift between position 2 and 3

[c] Terminal CH_2 (1,4 positions), +11.5 p.p.m.

Subject to these limitations the calibration plots of Fig. 1 may be employed to evaluate the local π-electron densities of other aromatic systems.

[4] J.N. Shoolery, J.Chem.Phys. 31, 1427 (1959).

[5] N. Muller and D.E. Pritchard, J.Chem.Phys. 31, 768 (1959).

Table 2

C^{13} and H^1 Chemical Shifts and π-Electron Densities of Azulene

(Chemical shifts in p.p.m. relative to benzene)

Position	$\delta_C{}^{13}$		J_{CH} (C/S)	$\delta_H{}^1$		ρ derived from		ρ calculated		
	Meas.	Corr.[a]		Meas.	Corr.[a]	$\delta_H{}^1$	$\delta_C{}^{13}$	Pariser[b]	Julg[c]	Brown[d] Heffernan
2	-6.7	-5.9	183	-0.583	-0.23	0.978	0.977	0.979	0.997	0.988
3,1	8.8	7.5	165	-0.067	+0.58	1.055	1.061	1.096	1.049	1.059
4,8	-8.9	-7.7	158	-0.945	-0.34	0.968	0.967	0.879	0.908	0.954
5,7	4.6	4.2	161	+0.280	+0.48	1.045	1.041	1.049	1.034	1.011
6	-8.9	-8.6	158	-0.170	-0.03	0.997	0.962	0.948	0.938	0.969
9.10								1.013	1.042	0.998

[a] Corrected for shift due to ring current of neighbour ring.

[b] R. Pariser, J.Chem.Phys. 25, 1112 (1956).

[c] A. Julg, J.Chim.Phys. 52, 377 (1955).

[d] R.D. Brown and M.L. Heffernan, Aust.J.Chem. 13, 38 (1960).

Table 2 shows the results obtained in this manner for the non-alternant hydrocarbon, azulene.[6] For comparison the calculated density values reported by several authors are shown in the last three columns. The relative C^{13} and H^1 shifts, as measured, are influenced by ring current circulation of the neighbor ring in the azulene molecule, and must be corrected. The corrected values, shown in Table 2, were obtained by employing a simple dipole approximation.[7] The overall accuracy of the final values is roughly estimated to be about 15%. There is a very close correspondence between the values derived independently from the H^1 and C^{13} resonances. The largest deviation (~4%) occurs at the 6-position, for which the C^{13} signal was not independently resolved and was overlapped by other signals. So far no satisfactory resonance signals have been obtained for the 9,10 positions, which may be due to unfavorable relaxation times for these particular nuclei. This point is being investigated.

The C^{13} resonance shift measurements of the aromatic ring systems were carried out on 2-3 molar solutions in tetrahydrofuran, except tropylium cation, which was measured as tropylium fluoroborate in aqueous solution containing some HBF_4 to prevent hydrolysis. Dimethylcarbonate enriched in C^{13} in the carbonyl group was used as an external reference. The azulene C^{13} resonance shifts were measured in a saturated solution of azulene in CS_2. The H^1 resonance shifts were measured in a 5 mole % solution of azulene in cyclohexane, the solvent signal serving as an internal reference. Measurement of a 5 mole % solution of benzene in cyclohexane in a similar manner permitted all shifts to be converted relative to benzene.

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[6] The C^{13} resonance shifts of azulene have recently been reported by Lauterbur [J.Amer.Chem.Soc. 83, 1838 (1961)] and correlated with the theoretically calculated charge densities in azulene.

[7] J.A. Pople, W.G. Schneider and H.J. Bernstein, High Resolution Nuclear Magnetic Resonance p. 254. McGraw-Hill, New York (1959).

Tetrahedron Letters No. 14, pp. 473-476, 1961. Pergamon Press Ltd. Printed in Great Britain.

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ABSENCE OF STERIC EFFECTS ON THE LEAVING GROUP IN S_N2 REACTIONS

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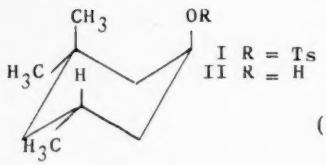
(Received 13 July 1961)

IT is well known,[1a] largely through the pioneering research of Polanyi and of Hughes and Ingold and their coworkers, that the rate of bimolecular nucleophilic displacement (S_N2) reactions is greatly retarded when there is steric hindrance to approach of the incoming nucleophile. In unimolecular nucleophilic displacement and elimination (S_N1-E_1) reactions there is no corresponding retardation; in fact recent work by H.C. Brown and by Bartlett and coworkers[1b,2] suggests that such reactions are subject to steric acceleration when the departure of the anion relieves strain in the starting molecule. It seemed to be of interest to investigate whether a corresponding steric acceleration could be produced in S_N2 reactions in cases where the departing group (but not the incoming group) were subject to steric compression.

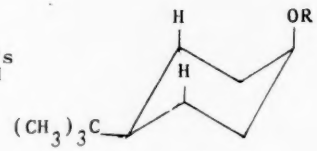
A suitable system for the purpose of such study is the trans-3,3,5-trimethylcyclohexyl system. In the tosylate (I) the leaving p-toluenesulfonate group is crowded by the axial methyl group, but there is no interference with the approach of the incoming nucleophile. The extent of crowding

[1] [a] cf. E.L. Eliel in M.S. Newman, Steric Effects in Organic Chemistry pp. 73-79; [b] pp. 70-73. John Wiley, New York (1956).

[2] For a contrary view, see D.V. Banthorpe, E.D. Hughes and C.K. Ingold, J.Chem.Soc. 4054 (1960).



I R = Ts
II R = H



III R = Ts
IV R = H

of the tosylate group may be inferred from the axial CH_3-OH-H interaction in the corresponding alcohol (II) which was recently measured[3] to amount to approximately 3.7 kcal/mole. The axial CH_3-OTs-H interaction is probably about the same, for the axial OTs-H-H interaction in cis-4-t-butylcyclohexyl tosylate (III)[4] and the OH-H-H interaction in the corresponding alcohol (IV)[4] both amount to about 0.6-0.8 kcal/mole.

Alcohol II is readily available from isophorone[3,5] and, contrary to a previous report,[6] is readily converted to the tosylate I, m.p. 67.5° by treatment with p-toluenesulfonyl chloride in pyridine at 0° (Found: C, 64.67; H, 8.37. $C_{16}H_{24}O_3S$ requires: C, 64.85; H, 8.17). Treatment of I (0.05 mole) with sodium thiophenolate (from 0.10 g atom Na and 0.146 mole PhSH) in 87% ethanol for 2 days gave 1.25 g (22%) of a fraction boiling at 38°/38 mm and 2.80 g (25%) of a fraction boiling at 126-130°/1.6 mm. The infrared spectrum and analysis of the low boiling fraction, n_D^{20} 1.4400 after percolation through alumina, were compatible with the expected 3,3,5- or 3,5,5-trimethylcyclohexene structure. (Found: C, 86.59; H, 12.97. C_9H_{16} requires C, 87.02; H, 12.98). The high-boiling fraction, presumably cis-

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[3] E.L. Eliel and H. Haubenstock, J.Org.Chem. In press.

[4] cf. E.L. Eliel, J.Chem.Educ. 37, 126 (1960). The values for the axial OH and OTs interactions have recently been confirmed in our laboratory by nuclear magnetic resonance spectroscopy, cf. E.L. Eliel, Chem. & Ind. 558 (1959).

[5] E.G. Peppiat and R.J. Wicker, J.Chem.Soc. 3122 (1955).

[6] I. Alkonyi, Chem.Ber. 92, 1130 (1959).

3,3,5-trimethylcyclohexyl phenyl sulfide, was oxidized to the sulfone, m.p. 135°, showing the characteristic sulfone bands at 1150 and 1300 cm^{-1} in the infrared. (Found: C, 67.70, 67.46; H, 8.30; 8.32. $C_{15}H_{22}O_2S$ requires: C, 67.65; H, 8.33).

It having been established that the reaction of I with thiophenolate in 87% ethanol does, in fact, give substitution and elimination rather than solvolysis products, the reaction was studied kinetically at 25.2°C under the conditions previously described.[7] Second-order kinetics were followed quite cleanly, the results being as follows:

Compound	NaSPh / ROTs	k (l/mole/sec. x 10^4)	k_s/k_e
I	1:1	6.97±0.10	0.348
	1:1	6.71±0.10	0.442
	1:2	6.65±0.14	0.477
	1:1	7.52±0.21	0.374
	1:2	6.88±0.26	0.380
I, average		6.95	0.404
III	1:1	7.84±0.10	0.833
	1:1	7.32±0.07	--
III, average		7.58	
III, lit.[8]		7.02	1.06

It is evident from the data that I reacts with thiophenolate at substantially the same overall rate as III, there being neither steric assistance nor steric hindrance of the reaction. In view of the fact that the steric compression energy in I would seem to exceed that in III by approximately 3 kcal/mole, this result is rather surprising. If the transition states for I and III had no compression energy due to the axial tosylate group left, the

[7] E.L. Eliel and R.G. Haber, J.Amer.Chem.Soc. 81, 1249 (1959).

strain relief in III would be ca. 0.7 kcal/mole and that in I ca. 2.8 kcal/mole (one CH_3-H interaction of about 0.9 kcal/mole is left over in I) so that I should react ca. 30 times faster than III at 25°. That there is, in fact, no appreciable difference between I and III at all must mean that whatever compression energy there is in the ground state persists to nearly the same extent in the transition state.

We believe that the merged mechanism of substitution and elimination[8,9] may account for the apparent small change in geometry of the leaving group between the ground state and the transition state in the thiophenolate displacement reaction of cyclohexyl tosylates as well as for the lack of correlation between the overall rate (nearly identical for I and III) and the ratio of substitution to elimination (about twice as large for III as for I).

Studies of solvolysis[10] and bimolecular elimination reactions of compound I as well as studies of the stereoisomeric cis-3,3,5-trimethylcyclohexyl system should throw further light on the problems raised here. Such studies are in progress in our laboratory.

We acknowledge, with thanks, support of this work by the National Science Foundation.

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[8] S. Winstein, D. Darwish and N.J. Holness, J.Amer.Chem.Soc. 78, 2915 (1956).

[9] E.L. Eliel and R.S. Ro, Tetrahedron 2, 353 (1958). See also ref. 7.

[10] cf. S. Nishida, J.Amer.Chem.Soc. 82, 4290 (1960).

Tetrahedron Letters No. 14, pp. 477-480, 1961. Pergamon Press Ltd. Printed in Great Britain.

SYNTHESIS OF A PENTACOVALENT ARSENIC HETEROCYCLE

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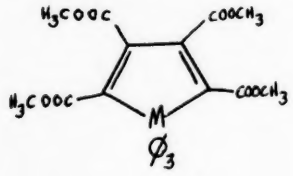
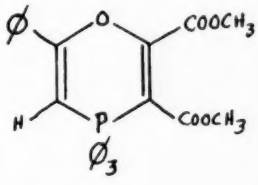
(Received 14 July 1961)

THE recent publication[1] of the preparation of a phosphole (Ia) containing pentacovalent phosphorus prompts us to report the results of similar research into heterocycles of pentacovalent fifth-row atoms containing five single bonds to carbon.[2] We have independently prepared the phosphole reported by Johnson and wish now to announce as well the arsenic analog (Ib). When triphenylarsine is mixed with a slight excess of pure dimethyl acetylene-dicarboxylate in ether and allowed to stand several days, the mixture deposits in over 50% yield white crystals of tetramethyl 1,1,1-triphenylarsole-2,3,4,5-tetracarboxylate (Ib), m.p. 212° (Found: C, 61.9; H, 4.9. Calc. for $C_{30}H_{27}AsO_8$: C, 61.0; H, 4.6%).[3] The infrared spectrum shows two ester peaks



Ia, M = P
b, M = As



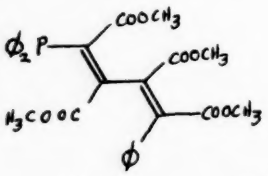
II

[1] Johnson and Tebby, J.Chem.Soc. 2126 (1961).

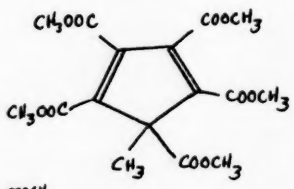
[2] J.B. Hendrickson, J.Amer.Chem.Soc. 83, 2018 (1961).

[3] The high carbon values in the analyses are apparently due to some arsenical trapped in the soda-lime trap, as shown by positive Gutzeit tests on the soda-lime.

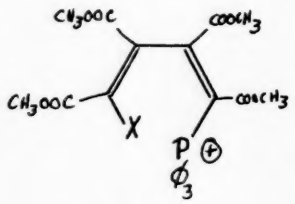
of about equal intensity at slightly different wavelengths (5.80 and 6.00), similar in this respect to the phosphole, Ia, and our recent oxaphosphorin, II[2], as well as to dimethyl 2,3-diphenylpyrrol-4,5-dicarboxylate.[4] The ultraviolet spectrum shows a large peak at 220 m (log ε = 4.63) and a family of three at 259 m (3.99), 264 m (3.99), and 270 m (3.88), very similar to the spectra of triphenylphosphine and arsine oxides[5] and tetraphenylphosphonium ion[6] but increased in intensity. The latter spectra are said to be little more than that expected from the multiple phenyl absorption and differ notably from the simple triphenyl compounds (ϕ_3P, ϕ_3As, etc.) which are trivalent and bear an unshared electron pair.[5] The spectrum of the phosphole, Ia, was not obtainable[1] owing to its ready reversion in solution to the stable rearrangement product, III.



III



IV



Va, X = -
b, X = H

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[4] J.B. Hendrickson and Rees, J.Amer.Chem.Soc. 83, 1250 (1961).

[5] Jaffe, J.Chem.Phys. 22, 1430 (1954).

[6] Unpublished observations.

These spectra are important for the light they throw on the bonding properties of the pentacovalent atoms, for the spectrum of the butadiene-tetra-ester portion of the molecule has been reported by Cookson[7] for his penta-ester, IV, which shows maxima at 223 mμ (log ε = 3.92) and 295 mμ (3.78). The shift from these values in the present compounds clearly requires some resonance participation by outer orbitals of the pentacovalent atom, despite the fact that the pentacovalency itself would be expected to afford complete saturation of the bonding capacity of these atoms.

Evidence for the attachment of the three phenyl groups to arsenic, apart from the mode of formation, is provided by the reaction of the heterocycle with ozone, followed by thiosulfate reduction and sublimation, which yielded authentic triphenylarsine, m.p. and mixed m.p. 59-61°. Similarly, warming with methanolic KOH saponified one ester group to a mono-acid, $C_{29}H_{25}AsO_8$ (Found: C, 61.08; H, 4.3. Calc.: C, 60.4; H, 4.34%),[3] which on pyrolysis yielded triphenylarsine oxide, m.p. 180-200° (subl.), identical in infrared spectrum to an authentic sample, as well as triphenylarsine, similarly identified. Diazomethane converted this acid back to the starting ester.

The nuclear magnetic resonance spectrum provides several features of interest for it consists of only three clean sharp peaks at τ = 2.78; 6.34; 6.87; with intensities of about 5:2:2. Thus the correspondence with expectation is striking. Triphenylarsine shows a clean peak at 2.92 whereas the peak of triphenylphosphine at the same place is split and complex owing to splitting of aromatic hydrogens (primarily ortho) by the phosphorus nucleus (nuclear spin 1/2),[2] a splitting not observed with the arsenic nucleus (nuclear spin 3/2). Accordingly, while the 2.78τ peak is clean in the arsole, Ib, it is split in the phosphole, Ia, centering at 2.70, as in the oxaphosphorin, II (2.65). The stable rearrangement product, III, shows the complex peak of

[7] R.C. Cookson, J. Hudec and Whitear, Proc.Chem.Soc. 117 (1961).

$\phi_2\overset{\cdot\cdot}{P}$-centering at 2.82 with the single phenyl bonded to the olefin absorbing at 2.44, reminiscent of the cinnamoyl absorption; all four ester methyls show up as separate peaks (6.08, 6.64, 6.67, and 6.98). The freshly-prepared unstable phosphole, Ia, always shows a complex absorption between τ = 6-7 containing these four peaks (increasing with impurity of the sample or with time) and two others at 6.31 and 6.37, as well as the unified complex ϕ_3P peak.

The thermal stability of this heterocycle is in remarkable contrast to that of the phosphole, which readily decomposes at room temperature,[1] for vacuum pyrolysis up to 300° served only to cause clean sublimation of the arsole. This thermal instability in the phosphorane case was offered[1] as one reason for its formulation as the acyclic zwitterion, Va, but the similarity of the other physical properties between the two compounds seems to us to provide a more compelling rationale for the true phosphole formulation, Ia. Furthermore, if a solution of the freshly-prepared phosphole in methanol is treated with HCl in methanol, an immediate precipitation of the stable rearrangement product, III, occurs. Since there is no reason to expect that the protonated form of the zwitterion, Vb, should not be a stable salt as it stands nor that it should rearrange instantly to III, the zwitterionic formulation seems untenable to us and we prefer Ia, rearrangement of which to III by acid catalysis (*cf.* initial protonation of a β-ester carbonyl) is mechanistically sound. The differences in stability are nevertheless so striking as to require explanation, for which we tentatively proffer the larger size of arsenic and the greater availability of low-energy d-orbitals for its bonding as reasons for the greater stability of Ib.

Further studies of these interesting heterocycles are in hand.

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RAUWOLFIA ALKALOIDS - XLII

METHYL NEORESERPATE, AN ISOMER OF METHYL RESERPATE. PART 4. INFRARED SPECTRA AND CONFIGURATION AT C-3

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(Received 17 July 1961)

IN connection with our studies of the structure[1] and mechanism of formation[2] of methyl neoreserpate, an isomer of methyl reserpate, we have examined the infrared spectra of a number of 16α-carbomethoxyl derivatives. We have found that these compounds are not in agreement with Wenkert's correlation[3] of infrared spectra with configuration at C-3, and propose that observed differences in the 2800 cm^{-1} region of the infrared spectrum reflect not changes in configuration, but changes in conformation at C-3. Our assignments of specific conformations to C-3 hydrogens are strongly supported by our studies of the NMR spectra of methyl reserpate, methyl neoreserpate, and methyl 3-isoreserpate.[4]

In the quinolizidine series, infrared bands in the 2700-2800 cm^{-1} region have been correlated with the presence of at least two α-hydrogen atoms trans coplanar (diaxial) to the electron pair on the bridgehead nitrogen.[5] This

[1] W.E. Rosen and J.M. O'Connor, J.Org.Chem. In press.

[2] W.E. Rosen and H. Sheppard, J.Amer.Chem.Soc. In press.

[3] E. Wenkert and D. Roychaudhuri, J.Amer.Chem.Soc. 78, 6417 (1956).

[4] W.E. Rosen and J.N. Shoolery, J.Amer.Chem.Soc. In press. The conformations are also consistent with infrared spectra, pKa measurements, and optical rotatory dispersion curves obtained by K. Nakanishi and F. Yamasaki [private communication; see F. Yamasaki, Nippon Kagaku Zasshi 82, 72 (1961)].

[5] F. Bohlmann, Angew.Chem. 69, 641 (1957); Chem.Ber. 91, 2157 (1958).

correlation has been applied successfully to similar systems,[6,7] including various alkaloids.[8,9,10] Prior to this correlation, Wenkert had suggested[3] that infrared bands in the 2800 cm^{-1} region could be used with indole alkaloids containing the ring system of yohimbine, ajmalicine, or corynantheine to distinguish between normal or allo derivatives (those possessing a 3α- hydrogen) and pseudo or epiallo derivatives (those possessing a 3β- hydrogen). The appearance of two characteristic infrared bands in chloroform spectra of all those alkaloids known to have a 3α- hydrogen, and its absence in spectra of those alkaloids known to have a 3β- hydrogen, suggested its use as an analytical method for assigning configuration at C-3 for new alkaloids. The application of this analytical method has proved useful,[11] although two exceptions (3-epialloyohimbone and 3-epialloyohimbine) have been reported.[12]

We feel that Wenkert's rule[3] for the chloroform spectra of indole alkaloids should be modified to: "All compounds possessing in their stable conformations axial hydrogens at C-3 exhibit two or more peaks or distinct shoulders between 2700-2900 cm^{-1} (at least one of which absorbs below 2800 cm^{-1}) on the low wave number side of the major (ca. 2900 cm^{-1}) band, whereas those containing equatorial hydrogens at C-3 do not". This modified rule does not explain differences in the position or the appearance of these extra peaks, but it points out that secure assignment of configuration at C-3 by infrared spectroscopy requires that the compound be fairly pure

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6 S. Ohki and Y. Noike, Chem.Pharm.Bull.Japan 7, 708 (1959).

7 N.J. Leonard and W.K. Musker, J.Amer.Chem.Soc. 82, 5148 (1960).

8 A.R. Battersby, R. Binks and G.C. Davidson, J.Chem.Soc. 2704 (1959).

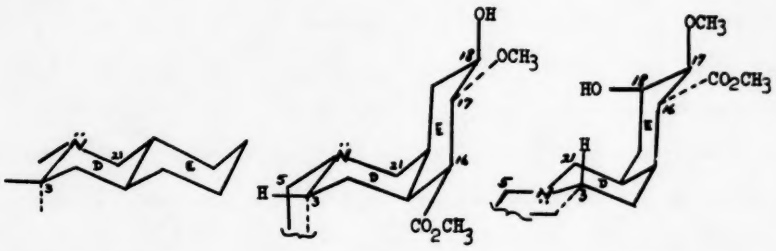
9 M. Terashima, Chem.Pharm.Bull.Japan 8, 517 (1960).

10 F. Bohlmann et al., Chem.Ber. 91, 2167, 2176, 2189, 2194 (1958).

11 N. Neuss and H.E. Boaz, J.Org.Chem. 22, 1001 (1957).

12 M.-M. Janot, R. Goutarel, E.W. Warnhoff and A. LeHir, Bull.Soc.Chim. Fr. 637 (1961).

conformationally, and that the relation between conformation and configuration be known. Application of the modified rule and recognition of its limitations will prevent the errors of assignment which might follow strict application of the original rule.



I II III

With D/E trans-locked alkaloids (partial formula I), the ring system requires that the 3α- substituent be axial and the 3β- substituent be equatorial, so that the modified rule leads to the same conclusion as the original rule. With D/E cis-locked alkaloids, however, two stable chair conformations (II and III) are possible. Methyl reserpate (partial formula II) and its derivatives (including 3-iso-derivatives) are stable in the conformation which has the 3α- substituent axial and the 3β- substituent equatorial with respect to ring D.[4] With methyl neoreserpate (partial formula III) and its derivatives, however, the 3α- substituent is equatorial and the 3β- substituent is axial in the stable conformation.[4] The derivatives of methyl neoreserpate show, as expected, characteristic extra peaks in the 2700-2900 cm^{-1} region. The so-called exceptions[12] to Wenkert's rule, 3-epialloyohimbone and 3-epialloyohimbine, are probably structurally similar to III. We have found, analogous to the 3-epialloyohimbone exception, that both alloreserpone and 3-epialloreserpone[1] show extra peaks in the 2700-2900 cm^{-1} region.

The modified rule proposed here is actually an application of the correlation described by Bohlmann.[5] With I and II, the ring system does not permit the hydrogen on C-5 to be trans diaxial to the nitrogen electrons unless the hydrogen on C-3 is axial; since systems I and II have either one axial hydrogen (on C-21) or three axial hydrogens (C-3, C-5, and C-21) trans to the nitrogen electrons, the infrared bands for two or more can be correlated with the C-3 hydrogen alone. With the ring system III, trans diaxial hydrogens at C-5 and C-21 are necessarily present when the 3β-hydrogen is present. The hypothetical 3α- hydrogen (equatorial) epimer of ring system III would have only one trans axial hydrogen (at C-21) and therefore would not show the characteristic infrared peaks.

The author thanks Mr. Louis Dorfman for helpful discussions.

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AN INVESTIGATION BY MASS SPECTROMETRY OF THE ALKALOIDS OF ASPIDOSPERMA QUEBRACHO-BLANCO

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Department of Chemistry, Massachusetts Institute of Technology, Cambridge, Mass.

(Received 2 July 1961)

In recent years many Aspidosperma species have been investigated chemically and a number of new alkaloids were found and shown to belong to three groups: derivatives of dihydroindoles, indoles, and pyridocarbazoles. The structures of most of these compounds have been elucidated recently.[1] The best known source of aspidosperma alkaloids is the bark of A. quebracho blanco Schlecht.,[2] which contains three alkaloids of known structure; namely, aspidospermine,[3,4] quebrachamine[5] and quebrachine (later found to be yohimbine[6]). In addition to these three alkaloids, Hesse had originally also isolated aspidospermatine, aspidosamine and hypoquebrachine. The existence of the three last-mentioned compounds, not well characterized, was doubted by some of the workers in the field.

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[1] For a review, see J. Schmutz, Pharm. Acta Helv. 36, 103 (1961).

[2] O. Hesse, Liebigs Ann. 211, 249 (1882).

[3] J. F. D. Mills and S. C. Nyburg, Tetrahedron Letters No. 11, 1 (1959).

[4] H. Conroy, F. R. Brook and Y. Amiel, Tetrahedron Letters No. 11, 4 (1959).

[5] K. Biemann and G. Spiteller, Tetrahedron Letters No. 9, 299 (1961).

[6] E. Fourneau and H. Page, Bull. sci. pharmacol. 21, 7 (1914).

Having available in mass spectrometry a very sensitive method which has proven useful in the elucidation of the structure of a number of indole alkaloids,[5,7-9] we undertook a reinvestigation of the alkaloids occurring in the bark of A. quebracho blanco relying mainly on aluminum oxide chromatography and gas chromatography for their separation, and on mass spectrometry and ultraviolet spectroscopy for the elucidation of their structure.

The extract from 300 grams of the powdered, dry bark after removal of neutral and acidic material consisted of 1.95 g , which turned out to be a complex mixture of alkaloids as indicated by a preliminary gas chromatogram and the mass spectra of some of the fractions. It was not possible to achieve a complete separation of the individual components because the isolation of the minor components in amounts sufficient for a good mass spectrum (a fraction of a milligram) necessitated the use of a relatively large amount of liquid phase (6% Apiezon L). Complete separation of all components by chromatography on alumina was also not possible, but further purification of the fractions by gas chromatography permitted the isolation of about twenty compounds in reasonable purity.

Table I lists, in the order of their emergence from the alumina column, fifteen of the compounds investigated in detail. The numbers denoting the components are their molecular weights as deduced from the mass spectra, which also indicated that there are present two groups of compounds designated A and B. Group A was recognized to be related to aspidospermine, the spectrum of which we had determined previously, and was identical with the spectrum of 342A. It has a very strong peak at m/e 124, and this peak

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[7] K. Biemann, Tetrahedron Letters No. 15, 9 (1960).

[8] K. Biemann and M. Friedmann-Spiteller, Tetrahedron Letters No. 2, 68 (1961).

[9] C. Djerassi, B. Gilbert, J. N. Shoolery, L. F. Johnson and K. Biemann, Experientia 17, 162 (1961).

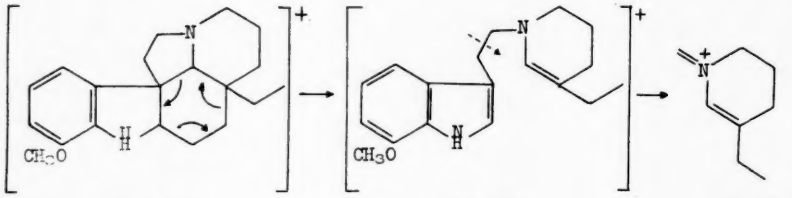
is found in the spectra of all alkaloids of Group A. Group B is characterized by a very intense peak at m/e 136 (138 in 340B). Quebrachamine and yohimbine were identified on the basis of their physical constants.

TABLE I

Compound	Yield[a] %	M. P.	Characteristic Peaks in the Mass Spectrum[b]
Quebrachamine	2.5	146-7	
296A	<.5	c	296; 268; 124
326A	<.5	c	326; 298; 124
280A	2.0	c	280; 251; 210
282A	<1.0	110-2	282; 254; 124
312A	3.0	109-11	312; 284; 124
Aspidospermine (354A)	30.0	208-9	354; 326; 124
384A	1.5	148-50	384; 356; 124
280B	<1.0	c	280; 136; 158[d]; 144[d]
266B	3.0	184-6	266; 136; 144; 130
296B	1.5	c	296; 136; 174; 160
308B	1.0	c	308; 136; 144; 130
338B	3.0	157-9	338; 136; 174; 160
340B	<1.0	c	340; 138; 174; 160
Yohimbine	10.0	223-5	

(a) in % of total bases. (b) for Group A and B only. (c) not crystalline. (d) These two columns are peaks due to the indole part of the molecules. Acyl groups are eliminated during fragmentation.

A discussion of the elucidation of the structure of the remaining twelve alkaloids, three of which turned out to be known derivatives of aspidospermine, follows. The characteristic peaks in the mass spectra of the alkaloids of Group A are summarized in Table I, and their relation to the structure of the molecule is shown below, using deacetylaspidospermine as an example:



312 (MW) 284 (Y) 124 (Z)

The molecular weight indicates the sum of all substituents attached to the basic carbon skeleton (I) and peak Y permits the conclusion that in none of the compounds is there a substituent on the two carbon bridge. The same conclusion can be drawn for the piperidine moiety of the molecules because additional groups there would change the mass of fragment Z.

It follows from the mass spectra that these alkaloids are substituted in the indole moiety of I by methyl, methoxyl, and acetyl groups, respectively. The methyl groups were placed on N_a because of the early emergence of these components from the alumina column. N_a-methyldeacetylaspidospermine[10] was synthesized and found to be identical (mass spectrum and retention time) with compound 326A. The mass spectra of 296A and 326A showed clearly that the two compounds differ only by a methoxyl group. Compound 312A, which must contain a methoxy group, was identified by melting point, mixed melting point, and mass spectrum as deacetylaspidospermine. Compound 384A according to its spectrum is substituted in the indole nucleus by two methoxyl groups and one acetyl group, which suggested it to be pyrifolidine.[9] It was not possible to separate this component from the major alkaloid of the group, aspidospermine, which has only one methoxyl group less. The fractions rich in 384A were hydrolyzed and the deacetyl derivatives were separated by chromatography. The

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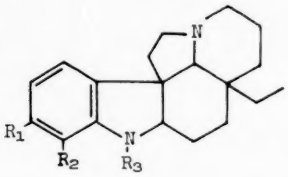
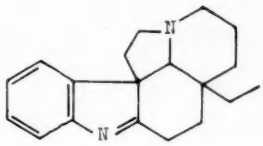
[10] B. Witkop and J. B. Patrik, J. Amer. Chem. Soc. 76, 5603 (1954).

fractions emerging after deacetylaspidospermine had m.p. 144-6° and gave a mass spectrum identical with the one of deacetylpyrifolidine. Upon reacetylation the product had $[\alpha]_D^{28}$ - 93° (chloroform) and is thus (-) pyrifolidine.

Finally, compound 282A does not contain any additional substituents and is, therefore, unsubstituted I. Compound 280A does not exhibit a strong peak at m/e 124 but was recognized to be related to Group A on the basis of its mass spectrum, which was identical with the spectrum of a compound (II) we had isolated earlier on zinc dust distillation of quebrachamine.[5] On reduction 282A was formed.



I



II

282A: I, $R_1 = R_2 = R_3 = H$ 326A: I, $R_1 = H$, $R_2 = CH_3O$, $R_3 = CH_3$

296A: I, $R_1 = R_2 = H$, $R_3 = CH_3$ 354A: I, $R_1 = H$, $R_2 = CH_3O$, $R_3 = CH_3CO$

312A: I, $R_1 = R_3 = H$, $R_2 = CH_3O$ 384A: I, $R_1 = R_2 = CH_3O$, $R_3 = CH_3CO$

The similarity of the mass spectra of Group B indicates that all these compounds contain the same carbon skeleton and differ in the substitution in the dihydroindole moiety, the presence of which is borne out by the UV spectra of 266B and 338B. There is also present a double bond as evidenced by an increase in the molecular weights by two mass units on hydrogenation and the shift of the most intense peak to m/e 138. While the mass spectra of Group B were somewhat reminiscent of the aspidospermine group, they could not have the same carbon skeleton because the characteristic loss of 28 mass units is not observed. Furthermore, the fragment of m/e 136 could not be merely a higher

homolog of the fragment of m/e 124 of Group A because the smallest molecule of Group B is 16 mass units lighter and not heavier than 282A. These findings can best be reconciled with the assumption of a one-carbon bridge in a ring system which on electron impact fragments into a highly stabilized indole system that remains connected to the rest of the molecule only by a single bond, the cleavage of which must give rise to the peak at m/e 136. Structure III would combine all these features, and only the C_2-group and the double bond remain to be placed. Structure IIIa seemed to be an attractive hypothesis, worth testing, but an authentic sample[11] exhibited a mass spectrum very similar but not identical with the spectrum of compound 266B. Since the difference seems to be due to either the location of the double bond or of the C_2-group, both substances were hydrogenated and the mass spectra of the products showed a molecular weight of 268 and a strong peak at m/e 138. The major difference was a peak at m/e 199 in IIIb and a peak at m/e 227 in dihydro-266B. This is best explained by cleavage at b in IV, which suggests structure IIIc for 266B, corroborated by the formation of 3-ethylpyridine on zinc dust distillation of a mixture of 266B and 296B, and by the UV spectrum of 266B (λ_{max} 242, 296 mμ; log ε 3.86, 3.49). The double bond is placed as shown on the basis of deuteration with deuterohydrazine[12] and the absence of a vinyl group according to the infra-red spectrum of 338B.

The major peaks in the mass spectra of the alkaloids of Group B again indicate the presence of methyl, methoxy, and acetyl groups on the indole moiety of 266B, the unsubstituted representative of this class. The structures of these compounds were deduced on the basis of the mass spectra as was done for the aspidospermine group. The position of the methoxyl group follows from the UV spectrum of 338B (λ_{max} 219, 255, 290(sh) mμ; log ε 4.54, 4.10, 3.62).

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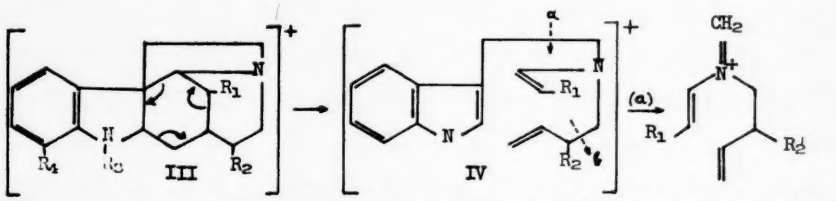
[11] G. F. Smith and J. T. Wrobel, J. Chem. Soc. 1960, 792

[12] Ng. Dingh-Nguyen and R. Ryhage, Arkiv f. Kemi 15, 433 (1960).



IIIa: $R_1 = R_3 = R_4 = H$, $R_2 = CHCH_3$ IIIc: $R_2 = R_3 = R_4 = H$, $R_1 = CHCH_3$

IIIb: $R_1 = R_3 = R_4 = H$, $R_2 = C_2H_5$ IIId: $R_2 = R_3 = R_4 = H$, $R_1 = C_2H_5$

266B: IIIc, $R_3 = R_4 = H$ 308B: IIIc, $R_3 = CH_3CO$, $R_4 = H$

280B: IIIc, $R_3 = CH_3$, $R_4 = H$ 338B: IIIc, $R_3 = CH_3CO$, $R_4 = OCH_3$

296B: IIIc, $R_3 = H$, $R_4 = OCH_3$ 340B: IIId, $R_3 = CH_3CO$, $R_4 = OCH_3$

Additional chemical evidence for these relationships within Group B was obtained by hydrolysis of 308B to 266B and of 338B to 296B, and by hydrogenation of 338B to 340B. While the mass spectrometric molecular weights were sufficient indication of the elemental composition of all the compounds reporte a C, H, N-analysis(correct for $C_{21}H_{26}N_2O_2$) was secured for 338B, the most important representative of Group B. Compound 338B has $[\alpha]_D^{27}$ - 73° (ethanol).

The melting point and the rotation of 338B are very close to the corresponding constants of aspidospermatine (m.p. 163°, $[\alpha]_D^{15}$ - 72°) [6] which Hesse had isolated almost eighty years ago. Although he suggests a formula $C_{22}H_{28}O_2N_2$ for which good C, H, and N values are present, it is possible that he actually had in hand the lower homolog, particularly since the analysis of the chloroplatinate of aspidospermatine definitely agrees better with a C_{21} formula. Since compound 338B is one of the more abundant minor alkaloids of this plant and also has a considerable tendency to crystallize in contrast to many other of the components which we have found, the identity of 338B with aspidospermatine is very likely.

The isolation of so many of the minor alkaloids of Aspidosperma quebracho blanco should have considerable significance for the biogenesis of these

alkaloids. We are inclined to believe that Group A is formed via a quebrachamine-type intermediate followed by ring closure to demethoxydeacetylaspidospermine (282A), which is then substituted in the dihydroindole moiety, particularly since we were unable to find any trace of substituted quebrachamines among these alkaloids. In the structure of the alkaloids of Group B we may have finally found the biogenetic link between the dihydroindole alkaloids of the genus Aspidosperma and ulein,[13] the major alkaloid of Aspidosperma ulei Mgf.

A more detailed account of this work and of the interpretation of the mass spectra will be presented in the full paper.

Acknowledgments - We are indebted to S. P. Penick and Company, New York, for a gift of quebracho bark and to the Petroleum Research Fund of the American Chemical Society and, in part, to The Upjohn Company for financial support. We thank Dr. G. F. Smith for a sample of IIIa.

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[13] G. Büchi and E. W. Warnhoff, J. Amer. Chem. Soc. 81, 4433 (1959).

Tetrahedron Letters No. 14, pp. 493-498, 1961. Pergamon Press Ltd. Printed in Great Britain.

THE SYNTHESIS OF THE dl-9-iso-PIMARADIENES AND THE REVISION OF THE STRUCTURES OF ISOPIMARIC ACID AND RIMUENE

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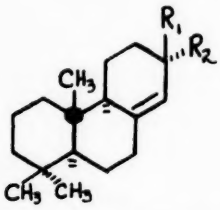
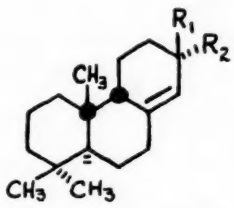
(Received 17 July 1961)

THE recently recorded[2] synthesis of dl-sandaracopimaradiene (1) and dl-pimaradiene (2) from this laboratory





(1) R_1=-CH_3; R_2=-CH=CH_2 (3) R_1=-CH_3; R_2=-CH=CH_2

(2) R_1=-CH=CH_2; R_2=-CH_3 (4) R_1=-CH=CH_2; R_2=-CH_3

established the stereochemistry of the corresponding resin acids, and showed that the structure first suggested[3] for the diterpenoid hydrocarbon rimuene - namely, sandaracopimaradiene (1) - was incorrect[4]. As a continuation of our

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[1] Sun Oil Company Fellow, 1959-1960.

[2] R. E. Ireland and P. W. Schiess, Tetrahedron Letters No. 25, 37 (1960).

[3] L. H. Briggs, B. F. Cain, B. R. Davis and J. K. Wilmhurst, Tetrahedron Letters No. 8,13 (1959); L. H. Briggs, B. F. Cain and J. K. Wilmhurst, Chemistry and Industry 599 (1958).

[4] The previously (V. Galik, J. Kuthan and F. Petrů, Chemistry and Industry 722 (1960)), claimed conversion of sandaracopimaric acid to rimuene has been found to be in error (private communication from F. Petrů).

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interest in methods of constructing the ring C substitution pattern of the pimaric acids, we have undertaken the synthesis of the 9-iso-pimaradienes (3) and (4), having the trans-syn-phenanthrene backbone. Interest in these structures was heightened recently by a preliminary report by Wenkert and Beak[5] "confirming" that rimuene was represented by the structure (4). A necessary assumption for this assignment was that isopimaradiene have the stereochemistry depicted in structure (3). We wish to report here the successful synthesis of the 9-iso-pimaradienes (3) and (4) and show that neither structure corresponds to rimuene or isopimaradiene.

Treatment of the unsaturated aldehyde (5)[6] with methyl lithium afforded an 85% yield of the alcohol (6), b.p. 105-106°/0.3 mm. (C, 80.89%; H, 11.75%). Equilibration[7] of this alcohol with ethyl vinyl ether and pyrolysis[8] of the resulting vinyl ether afforded an aldehyde[9] (acid (Ag_2O), m.p. 150-151°, C, 77.19%; H, 10.53%) which was protected as the acetal (7), b.p. 110°/0.2 mm. (C, 77.97%; H, 11.12%) in an overall yield 53%. On hydroboration[10] and oxidation

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5 E. Wenkert and P. Beak, J. Amer. Chem. Soc. 83, 998 (1961).

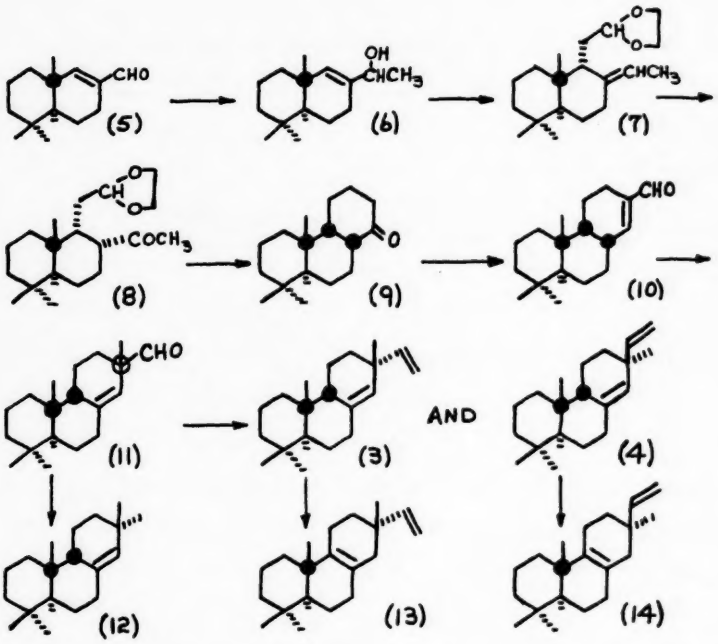
6 R. F. Church, R. E. Ireland and J. A. Marshall, Tetrahedron Letters No. 1, 34 (1961).

7 W. H. Watenabe and L. E. Conlon, J. Amer. Chem. Soc. 79, 2828 (1957).

8 A. W. Burgstahler and I. C. Nordin, J. Amer. Chem. Soc. 83, 198 (1961).

9 The stereochemistry of an aldehyde prepared in a similar fashion has been recorded[6].

10 H. C. Brown, K. L. Marray, L. J. Murray, J. A, Snover and G. Zweifel, J. Amer. Chem. Soc. 82, 4233 (1960).



the keto acetal (8), m.p. 132-133.5° (C, 73.83%; H, 10.57%) was obtained in 60% yield. Acid cleavage of the acetal function and cyclization of the resulting aldehydoketone afforded a tricyclic α,β-unsaturated ketone, m.p. 116-117° ($\lambda_{max.}^{95\%EtOH}$ 227 mu (E 8500); C, 82.75%; H, 10.44%) in 65% yield. On catalytic hydrogenation the saturated tricyclic ketone (9), m.p. 78-79.5° (C, 82.28%; H, 11.38%) was obtained in quantitative yield. Confirmation for the β-configuration of the 9-hydrogen atom was found in the non-identity of the ketone (9) with the trans-anti-trans-isomer, m.p. 78-80°, prepared in our earlier work[2] (infrared spectral comparison; depression of the melting point to 47-65° on admixture).

Introduction of the 13-methyl-13 vinyl substituents was

accomplished essentially as outlined previously[2] by conversion of the ketone (9) via the n-butylthiomethylene derivative[11] (m.p. 73-74°; C, 75.83%; H, 10.30%; S, 9.32%), and the α,β-unsaturated aldehyde (10), m.p. 107-109° (C, 83.08%; H, 10.91%) to the methylated aldehydes (11) in 43% overall yield, while separation of the epimeric aldehydes (11) by column chromatography proved unsatisfactory, pure samples of the 13-vinyl derivatives (3) (C, 87.93%; H, 11.76%) and (4) (C, 88.08%; H, 11.76%), prepared in quantitative yield from the aldehydes (11) by treatment with methylenetriphenylphosphorane[12], were readily available by preparative gas-liquid chromatography. When each diene was treated separately with dry hydrogen chloride in dry chloroform[13] rearrangement of the nuclear double bond occurred, and the diene (3) afforded dl-$\Delta^{8(9)}$-sandaracopimaradiene (13)[14] (C, 88.12%; H, 11.92%), while the diene (4) yielded dl-$\Delta^{8(9)}$-pimaradiene (14)[14] (C, 88.05%; H, 11.75%), thus establishing the configuration at C(13) in the dienes (3) and (4). The NMR spectrum of the olefin (12) (C, 87.51%; H, 12.43%) (prepared by Wolff-Kishner reduction of the mixture of epimeric aldehydes (11)) showed a single, uncoupled vinyl hydrogen signal at 5.30τ, thereby confirming the presence of a $\Delta^{8(14)}$-double bond in the dienes

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11 R. E. Ireland and J. A. Marshall, J. Amer. Chem. Soc. 81, 6336 (1959).

12 G. Wittig and V. Schöllkopf, Ber. 87, 1318 (1954).

13 O. E. Edwards and R. Howe, Canad. J. Chem. 37, 700 (1959).

14 Each of the reference $\Delta^{8(9)}$-derivatives was prepared in a similar fashion in this laboratory from authentic samples of the corresponding pimaradiena.

(3) and (4). These observations coupled with the already demonstrated trans-syn-cis-phenanthrene skeleton of the ketone (9) conclusively establish the structure and stereochemistry of the dienes (3) and (4) as shown.

The lack of correspondence of the infrared spectra and mobility on gas-liquid chromatography of the diene (3) and isopimaradiene[15], and the diene (4) and rimuene emphasized the incorrectness of the formulations of the natural substances.

These results necessitated a re-examination of the structures of rimuene and isopimaradiene, and it was found that these materials cannot be C(13) epimers as suggested[5], since (a) isopimaradiene is readily rearranged by dry hydrogen chloride to $\Delta^{8(9)}$-sandaracopimaradiene (13) while rimuene is unaffected by acid treatment; and (b) the behavior of rimuene and isopimaradiene on gas-liquid chromatography is inconsistent with their being only C(13) epimers and further suggests that isopimaradiene has the trans-anti-structure rather than the trans-syn-formulation now accepted (see Table I).

Table I

Relative Mobility of Dienes on Gas-Liquid Chromatography

Rimuene	0.72	Pimaradiene	0.89
Diene (3)	0.74	Sandaracopimaradiene	1.00 (ref. std.)
Diene (4)	0.89	Isopimaradiene	1.23

The observed acid-stability of rimuene suggests that it is a structural isomer of the pimaradienes rather than a

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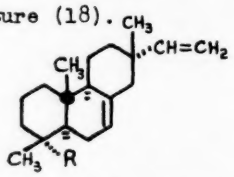
15 Prepared from isopimaric acid by the same sequence of reactions reported[2] earlier for sandaracopimaradiene and pimaradiene.

stereoisomer, as claimed[5]. On the other hand the acid-lability of isopimaradiene demonstrates its close relationship to the other pimaradienes. Inspection of the NMR spectrum of dihydroisopimaradiene (C, 87.73%; H, 12.38%) reveals two distinctive features not present in the spectra of the related dihydrodienes: (a) the presence of a broad, spin-coupled vinyl hydrogen signal at 5.03τ (also evident in the NMR curve recorded for methyl isopimarate by Wenkert and Beak[5]) and (b) a strong signal at 8.32τ best accomodated by the $-C{=}C-\underline{C}H_2-CR_3$ system. On the basis of these results and consideration of the proposed biogenesis of the resin acids[16], we suggest that isopimaradiene is represented by structure (17) and hence isopimaric acid by structure (18).



(17) R=-CH_3 (18) R=-CO_2H

This structure is consistent with all the previous results recorded on isopimaric acid[17] except the ozonolysis experiments[18], for which there is no ready explanation. Experiments designed to obtain further chemical verification of this structural assignment are underway at present.

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16 A. J. Birch, R. W. Richards, H. Smith, A. Harris and W. B. Whalley, Tetrahedron 7, 241 (1959).

17 A. K. Bose and W. A. Struck, Chemistry and Industry 1628 (1959); also see Edwards and Howe[14] for a summary of earlier reports.

18 G. C. Harris and T. F. Sanderson, J. Amer. Chem. Soc. 70, 2081 (1948).

Tetrahedron Letters No. 14, p. 499, 1961. Pergamon Press Ltd. Printed in Great Britain.

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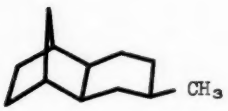
ERRATUM

PAUL von R. SCHLEYER and ROBERT D. NICHOLAS: Further examples of the adamantane rearrangement, Tetrahedron Letters No. 9, 305 (1961).

A methyl group was inadvertently omitted from Fig. IX, which should read



Tetrahedron Letters No. 15, pp. 501-505, 1961. Pergamon Press Ltd. Printed in Great Britain.

BIOGENETIC INTERRELATIONSHIPS OF ERGOT ALKALOIDS

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(Received 24 July 1961)

THERE is now good evidence for the fact that tryptophan[1,2] and tryptophan precursors[3] as well as mevalonic acid[4,5,6] and isopentenyl pyrophosphate[3] serve as precursors of the ergoline portion of the ergot alkaloids. As the next step in the elucidation of the biogenesis of these alkaloids, it appeared logical to establish their biogenetic kinship, suggestions for which have been put forth.[7,8] Allowing the fungus to act on C-14-labeled clavine alkaloids, we have now found living ergot to bring about the following conversion:

agroclavine ⟶ elymoclavine ⟶ penniclavine

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[1]D. Gröger, H. J. Wendt, K. Mothes, F. Weygand, Z. Naturf. 14b, 355 (1959)

[2]W. A. Taber and L. C. Vining, Chem. and Ind. 1218 (1959); and others

[3]H. Plieninger, R. Fisher, et al., Liebigs Ann. Chem. 642, 214 (1961)

[4]A. J. Birch, B. J. McLoughlin, H. Smith, Tetrahed. Letters No. 7, 1 (1960)

[5]D. Gröger, K. Mothes, H. Simon, H.-G. Floss and F. Weygand, Z. Naturf. 15b, 141 (1960)

[6]E. H. Taylor and E. Ramstad, Nature 188, 494 (1960)

[7]H. Rochelmeyer, Pharm. Ztg. 103, 1269 (1958)

[8]M. Abe, A Consideration Concerning the Biosynthesis of Ergot Alkaloids, 1960, Osaka, Japan

In the present investigation ergot strain 47 A, originally isolated from Pennisetum typhoideum, was used. It produces clavine-type alkaloids and small amounts of lysergic acid. It was grown in darkness on a sterilized medium consisting of 1% yeast extract and 1% glucose in tap water. On this medium, 47 A rapidly synthesizes alkaloids that are largely of the oxidized type. Labeled clavine alkaloids were produced in flasks containing 40 ml of medium by addition of 20 μC of mevalonic acid-2-C-14 ten days after inoculation with the organism. Two weeks later the cultures were harvested and the extracted alkaloids were chromatographed on formamide-impregnated Whatman-3-MM paper with benzene-pyridine (6:1) as the mobile phase.[9] The alkaloids produced by strain 47 A were separated by this system in the following sequence: secaclavine (chanoclavine), unknown-1, unknown-2, penniclavine, elymoclavine, lysergol, isopenniclavine, unknown-3, setoclavine, agroclavine and isosetoclavine. The major alkaloids, viz. elymoclavine, penniclavine, agroclavine, and isopenniclavine, were eluted separately and purified, and each alkaloid (spec. activities 0.51 - 1.47 x 10^6 d.p.m./mg) was dissolved in 5.00 ml of 0.25% aqueous succinic acid. Aliquots of each radioactive solution were introduced by means of a Millipore Hypodermic Adapter equipped with sterile filter into flasks containing 15 ml of culture medium that had been inoculated 9-12 days earlier with strain 47 A. For each alkaloid an aliquot of the solution was also introduced into a flask containing sterile medium alone (=blank) to serve as a check on the sterility of the introduced solution and on any possible conversion of the introduced alkaloid by the medium itself. Ten to twenty days after the introduction of the single labeled alkaloid, the resulting alkaloid mixture (250 - 500 γ / culture

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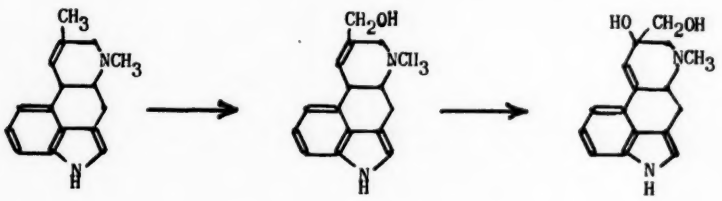
[9] M. Pöhm, Arch. Pharm. 291, 468 (1958)

flask) was extracted and, after chromatographic separation of the mixture, the total radioactivity of each individual alkaloid was determined with a Forro Radiochromograph. Benzoic acid-C-14 was used as a standard both for the calibration of the chromatogram scanner and for the counting with a Tri-Carb Liquid Scintillation Spectrometer. Quantitative estimations of the individual alkaloids were carried out according to the method of Pöhm and Fuchs,[10] the absorbance being measured at 550 mμ in the case of agroclavine and elymoclavine, and at 400 mμ in the case of penniclavine and isopenniclavine.

The table illustrates the distribution of radioactivity (per 0.5 ml of introduced alkaloid solution) among the alkaloids recovered from blank and from each 47 A culture.

Exposure of labeled agroclavine in the liquid medium to the alkaloid-producing ergot strain gave rise to labeled elymoclavine, labeled penniclavine and labeled isopenniclavine, whereas exposure of radioactive elymoclavine to the same treatment caused formation of radioactive penniclavine and isopenniclavine but not of radioactive agroclavine. Labeled penniclavine and isopenniclavine did not give rise to radioactive elymoclavine nor to radioactive agroclavine. The following biogenetic scheme is thus well supported by our experimental findings:



Agroclavine Elymoclavine Penniclavine
Iso-penniclavine

[10] M. Pöhm and L. Fuchs, Naturwiss. 40, 244, (1953)

DISTRIBUTION OF RADIOACTIVITY FROM 0.50 ml INTRODUCED ALKALOID SOLUTION AMONG RECOVERED ALKALOIDS

Introduced Labeled Alkaloid	Exposed to	Recovery of Radio-activity in Percent of Blank	Radioactivity of Isolated Alkaloids d.p.m.			
			Agro-clavine	Elymo-clavine	Penni-clavine	Isopenni-clavine
Agroclavine	Blank	100.0	12,650	< 200	< 200	< 200
	Medium+47 A	51.2	1,230	2,350	1,900	680
Agroclavine	Blank*	100.0	18,200	< 200	< 200	< 400
	Medium+47 A*	58.0	400	7,140	1,230	730
	Medium+47 A*	57.7	300	8,540	1,230	530
Elymoclavine	Blank	100.0	< 200	14,550	< 400	< 300
	Medium+47 A	41.2	< 200	2,500	2,790	740
	Medium+47 A	42.0	< 200	2,360	3,010	560
Elymoclavine	Blank*	100.0	< 400	21,950	< 400	< 300
	Medium+47 A*	59.6	< 200	10,300	1,820	850
Penni- and Isopenni-clavine	Blank	100.0	< 200	< 300	6,620	2,000
	Medium+47 A	59.5	< 200	< 200	2,950	1,380
	Medium+47 A	51.8	< 200	< 200	2,800	1,320

*An elymoclavine-accumulating medium consisting of 1% yeast extract and 2% glucose in tap water.

The total recovery of alkaloidal radioactivity from the blanks amounted to 88.8 - 96.4% of the introduced activity.

We found no reversibility of these reactions under our experimental conditions.

A considerable net loss in radioactivity occurred in the experiments. However, the possibility of a breakdown of the radioactive alkaloids followed by a re-incorporation of radiolabel from the breakdown products into the new alkaloids is very unlikely since, in the experiments with labeled elymoclavine, no incorporation into agroclavine had occurred, and with penniclavine, no incorporation into agroclavine or elymoclavine.

Preliminary conversion experiments with labeled elymoclavine indicate that some of the deficit radioactivity is present in lysergic acid, which was not extracted by the above method.

Acknowledgements: This investigation was supported by a grant from The National Institutes of Health, Contract No. RG-6606. We wish to express our appreciation to Dr. V. E. Tyler Jr., College of Pharmacy, University of Washington, for the culture 47 A and to Dr. A. Hofmann, Sandoz, Ltd., Basel, and Dr. M. Abe, Takeda Pharmaceutical Industries, Ltd., Osaka, for samples of pure ergot alkaloids, and to Mr. Adjit Shirodkar for technical assistance.

Tetrahedron Letters No. 15, pp. 506-512, 1961. Pergamon Press Ltd. Printed in Great Britain.

PRINCIPE ET APPLICATIONS D'UNE NOUVELLE METHODE DE DETERMINATION DES CONFIGURATIONS DITE "PAR DEDOUBLEMENT PARTIEL"

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(Received 24 July 1961)

LE problème de la détermination de la configuration absolue peut être abordé de plusieurs facons : Prelog[1] notamment lui a apporté une solution élégante qui résulte de l'interprétation de l'influence stérique dans la synthèse asymétrique.

La présente note décrit une nouvelle méthode, dite "par dédoublement partiel", basée sur les différences de réactivités liées à l'empêchement stérique.

On sait qu'un énantiomorphe A peut réagir avec des vitesses différentes sur chacun de deux antipodes optiques D et L d'un autre composé B; si donc, on met en réaction, en milieu homogène, une molécule de A avec un mélange, d'une molécule de D et d'une molécule de L, c'est-à-dire avec deux molécules de racémique, on peut s'attendre, après la fin de la réaction, à trouver dans la portion non combinée un excès d'un antipode par rapport à l'autre, ce qui constitue un dédoublement partiel.

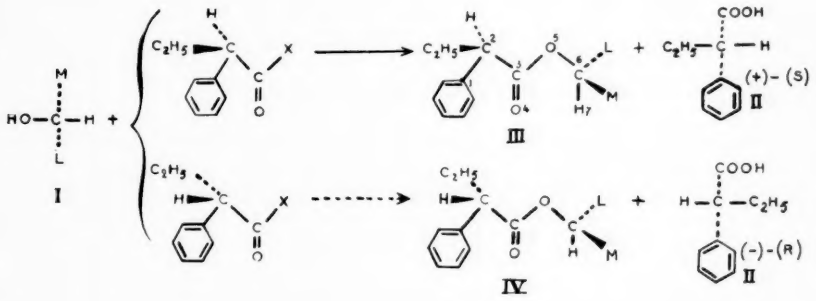
On peut illustrer ce fait, dans le cas de l'estérification par exemple, par une expérience simple en dissolvant dans la pyridine une molécule de

[1] V. Prelog, Helv.Chim.Acta 36, 308 (1953) et mémoires suivants.

l-menthol et deux molécules de chlorure de l'acide α phényl butyrique racémique C_6H_5-CH(C_2H_5)-COCl: après réaction, hydrolyse par un peu d'eau, élimination sous vide du solvant, on reprend par l'éther et la soude diluée: la phase alcaline apparait alors dextrogyre, ce qui ne peut être du qu'à la présence d'acide actif.

Connaissant la configuration absolue de l'antipode qui apparait et par conséquent de celui qui réagit préférentiellement, on peut en déduire la configuration absolue de l'alcool luimême.

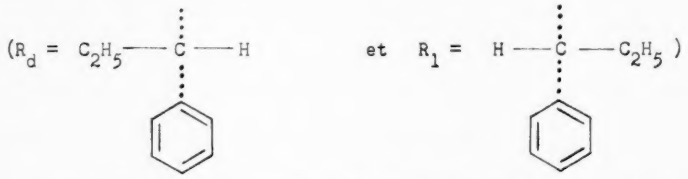
En effet, l'analyse conformationnelle de l'ester qui se produit en plus grande quantité à partir de l'alcool de configuration I indique qu'il s'agit de la structure III (l'ester moins abondant a la structure IV). Pour la structure favorisée III, on trouve, dans le plan du papier, les atomes numérotés de 1 à 7, en avant le radical éthyle de l'acide et le substituant M (medium) de l'alcool examiné et en arrière l'atome d'hydrogène de l'acide et le substituant L (large) de l'alcool examiné.



Dans le Tableau 1 ci-dessous, figurent quelques résultats (parmi de nombreux autres) obtenus avec des alcools secondaires appartenant à des séries les plus diverses et qui, tous, se comportent comme il vient d'être indiqué, compte-tenu de la configuration absolue des acides α phényl butyriques droit et gauche.[2,3,4]

L'anhydride de l'acide α phényl butyrique conduit à des dédoublements partiels beaucoup plus importants que le chlorure d'acide et c'est lui qui a été utilisé dans ces expériences.

Remarquons tout d'abord que cet anhydride peut exister sous trois formes: la forme méso R_d-CO-O-CO-R_l (V) et les deux formes énantiomorphes R_d-CO-O-CO-R_d (VI), R_l-CO-O-CO-R_l (VII)



Si nous supposons la réaction totalement stéréospécifique pour aboutir à l'ester de l'acide droit et si l'anhydride que nous faisons réagir est la forme racémique, nous avons l'équation (1):

$$R_d\text{-CO-O-CO-}R_d + R_l\text{-CO-O-CO-}R_l + R'OH \quad R_dCO_2R' + R_dCO_2H + R_lCO\text{-O-CO-}R_l \qquad (1)$$

Si, au contraire, l'anhydride existe sous la forme méso, nous aurons l'équation (2):

$$2\ R_d\text{-CO-O-CO-}R_l + R'OH \longrightarrow R_dCO_2R' + R_lCO_2H + R_dCO\text{-O-CO-}R_l \qquad (2)$$

Lorsqu'on hydrolyse l'anhydride en excès, on voit que le bilan final est le même que l'on parte de l'une ou l'autre des équations précédentes:

$$R_dCO_2R' + R_dCO_2H + 2R_lCO_2H$$

soit, dans les deux cas, une lecture correspondant à une molécule de R_lCO_2H.

Au contraire, lorsqu'en fin de réaction, on méthanolyse l'anhydride, on

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[2] B. Sjöberg, Acta Chem.Scand. 14, 281 (1960).

[3] P.A. Levene, R.E. Marker et A. Rothen, J.Biol.Chem. 100, 589 (1933).

[4] A. Rothen et P.A. Levene, J.Chem.Phys. 7, 975 (1939).

Tableau 1

	Substance	Déviation lue	Déviation théorique pour une estérification et un dédoublement complet	Rendement de l'estérification (%)	Rendement optique (%)	Configuration du carbone considéré[5]
1	(-) Menthol	+0,25°	0,67°	98	38	3 R
2	(-) Isobornéol	+0,20°	0,38°	85	62	2 R
3	(+) Bornéol	-0,72°	1,54°	93	50	2 S
4	androstanolone ou 17β-hydroxy 3-oxo(5α) androstane	-0,27°	0,58°	88	53	17 S
5	3 méthyloestradiol ou 3 méthoxy-17β-hydroxy oestra 1,3,5 (10) triene	-0,69°	1,6°	76	57	17 S
6	Testostérone ou 17β-hydroxy 3-oxo pregna 4-ène	-0,67°	1,6°	# 90	52	17 S
7	17α-hydroxy 3-oxo pregna 4-ène	+0,14°	0,50°	# 90	31	17 R
8	α amyrine	-0,19°	0,40°	# 60	79	3 S
9	(+) Tartrate diéthylique	+0,23°	1,6°	# 100	14	R R
10	(-) Malate diéthylique	-0,43°	1,97°	# 95	23	S
11	Codéine	-0,36°	1,55°	98	24	6 S
12	$20\alpha_F$-hydroxy(5α) prégnane	-0,12°	0,50°	93	26	20 S
13	$20\beta_F$-hydroxy(5α) prégnane	+0,10°	0,42°	93	26	20 R
14	3-méthoxy 17α hydroxy(14β) oestra 1,3,5(10)6,8 pentaène	+0,84°	2,25°	92	40	17 R

[5] Désignation spécifique de la configuration suivant R.S. Cahn, C.K. Ingold et V. Prelog, Experientia 12, 81 (1956).

a dans le cas de (1) le bilan suivant:

$$R_dCO_2R'+R_dCO_2H+R_1CO_2H+R_1CO_2CH_3$$

et dans le cas de (2):

$$R_dCO_2R'+R_1CO_2H+1/2R_1CO_2H+1/2R_dCO_2CH_3+1/2R_dCOOH+1/2R_1CO_2CH_3.$$

En d'autres termes, il ne doit plus y avoir de rotation dans le premier cas; dans le second, elle est identique à celle qu'on a lue après le traitement par l'eau.

L'expérience nous montre que, si, après réaction de l'anhydride sur un alcool optiquement actif, la solution brute est partagée en deux parties égales et reprise l'une par l'eau, l'autre par le méthanol, le pouvoir rotatoire de l'acide α phényl butyrique isolé est sensiblement le même dans les deux cas. Ce résultat prouve que la forme méso prédomine très largement dans l'anhydride utilisé.

D'autre part, on obtient un dédoublement partiel important en employant une seule molécule d'anhydride pour une molécule d'alcool actif: par exemple avec le l-menthol, le rendement optique est de 36%. Dans les mêmes conditions, avec deux molécules d'anhydride, le rendement optique est de 38% et de 40% avec trois molécules: ceci ne peut s'expliquer que si c'est la réaction (2) qui est en cause. On comprend d'ailleurs que la prédominance de la forme méso R_d-CO-O-CO-R_1 de cet anhydride rende son emploi beaucoup plus efficace que celui du chlorure d'acide racémique $R_dCOCl + R_1COCl$. En effet, dans ce dernier cas, il se produit, au cours de la réaction, une diminution de la proportion relative de l'antipode attaqué préférentiellement, alors que, dans le premier cas, le rendement optique est théoriquement indépendant de la quantité d'anhydride utilisé puisque la composition du réactif ne varie pas.

Ces considérations sont cependant insuffisantes pour expliquer la

supériorité de l'emploi de l'anhydride sur le chlorure d'acide: avec le l-menthol par exemple et le chlorure d'acide, le rendement optique n'est que de 3,5%. Une réponse à cette question ne pourra être apportée que par une étude plus approfondie du mécanisme des deux réactions et des états de transitions qu'ils impliquent.

Voici le détail d'une expérience:

A 7,4 mg de (-) isobornéol sont ajoutés 0,15 cc d'une solution pyridinique contenant 47,3 mg d'anhydride α phényl-butyrique. Après 15 heures, on verse dans un décanteur contenant du benzène et de l'eau et on titre en présence de phtaléine par la soude N/10. Consommé: 2,64 cc de soude N/10, théorie 3,05 cc; rendement de l'estérification 85%. La phase aqueuse acidifiée est extraite au benzène* lequel est concentré à 1 cc. Rotation lue sous 0,5 dm = + 0,20° pour la raie D; rendement optique = 62%.

L'examen des résultats montrent que les rendements optiques sont d'autant plus élevés que la différence d'encombrement sur les atomes de carbone qui entourent de part et d'autre la fonction alcool secondaire est plus grande. Les alcools épimères donnent évidemment des rotations de signes contraires (voir 2 et 3, 6 et 7, 12 et 13).

En possession de cet ensemble de résultats, on peut énoncer la règle empirique suivante: Dans les conditions que nous avons décrites, quand on obtient l'acide α phénylbutyrique droit, l'alcool secondaire est tel qu'un observateur ayant les pieds sur l'atome d'hydrogène et la tête sur l'hydroxyle voit le carbone "le plus encombré"** à gauche (et réciproquement).

Le résultat obtenu avec le tartrate d'éthyle, dont la configuration

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* L'acide α phényl butyrique possède une rotation dans le benzène de $\alpha_D = \pm 96,5°$, mais la rotation de son sel de sodium n'est que le dixième; par ailleurs à 280 mμ la rotation de l'acide est dix fois supérieure à celle qui correspond à la raie D. Il y a là une possibilité d'augmenter considérablement la sensibilité de la méthode.

** Ou, d'une manière plus générale "l'encombrement" quand il s'agit d'une molécule contenant plusieurs atomes de carbone asymétriques; dans ce cas, les conclusions doivent être prudentes et appuyées sur l'examen des modèles.

absolue a été déterminée d'une manière directe par Bijvoet,[6] peut être pris comme référence en admettant que le groupement $-COOC_2H_5$ est plus encombrant que l'ensemble $-CHOH-COOC_2H_5$; la configuration du l-malate d'éthyle découle immédiatement du signe de la rotation obtenue. (Expérience 10.)

Cependant, connaissant la configuration absolue d'une molécule complexe, il est possible de déterminer, de la même façon, l'orientation d'une substitution hydroxylée. Par exemple: les configurations α_F et β_F des 20-hydroxyprégnanes* peuvent être déduites immédiatement du signe de la rotation obtenue dans le dédoublement partiel (expériences 12 et 13). L'hydrogénation par le borohydrure de sodium de l'éther méthylique de l'isoéquilénine fournit un carbinol, F = 111°-112°, $[\alpha]_D$ = +43° (C = 0,35 dioxanne) (Trouvé: C 80,6; H 7,6. Calculé pour $C_{19}H_{22}O_2$: C 80,8; H 7,85) dont la configuration 17 α est prouvée par le résultat de l'expérience 14.

Cette méthode qui utilise des quantités très faibles de composés hydroxylés est applicable, comme on a pu le remarquer, à des molécules contenant des groupements (cétones, esters) réagissant sur les magnésiens.

Nous pensons pouvoir en généraliser le principe et l'étendre à d'autres fonctions.

Je remercie Mlle. Andrée Nouaille pour l'aide qu'elle m'a apportée dans l'exécution de ces expériences.

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* Je remercie vivement le professeur Klyne qui m'a envoyé, entre autres, 10 mg de chacun de ces alcools secondaires.

6 J.M. Bijvoet, A.F. Peerdeman et A.J. Van Bommel, Nature,Lond. 271 (1951).

Tetrahedron Letters No. 15, pp. 513-515, 1961. Pergamon Press Ltd. Printed in Great Britain.

THE CATALYTIC ACTION OF METAL SALTS ON THE BOROHYDRIDE REDUCTION OF α-BROMOKETONE

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ALTHOUGH sodium borohydride reduction of α-bromoketones usually affords bromohydrins,[1] in some cases debrominated products are obtained. For example, Henbest et al.[2] treated 3β-acetoxy-9α-bromoergostane-11-one with sodium borohydride and obtained a debrominated compound, 3β-acetoxyergostane-11-one; they suggested a mechanism involving initial hydride attack on bromine atom.

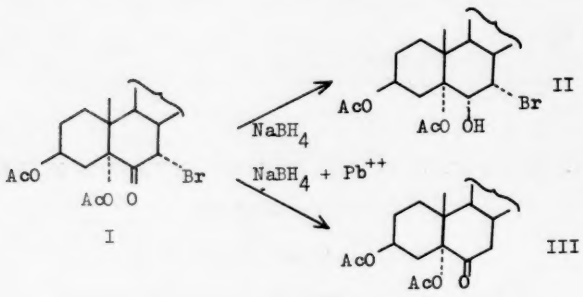
We wish to report a new finding that only a trace of lead ion alters completely the course of borohydride reduction of an α-bromoketone and gives a debrominated compound instead of the expected α-bromohydrin.

When treated with sodium borohydride in purified[3] methanol-dioxane, 7α-bromocholestane-3β,5α-diol-6-one diacetate (I) gave exclusively 7α-bromocholestane-3β,5α,6α-triol 3,5-diacetate (II). The front-side attack of a hydride ion on the bromoketone (I) would be due to a large steric hindrance of the bulky 7α-bromine and 5α-acetoxyl groups. When added a trace of lead acetate in the reaction mixture, the product obtained was cholestane-3β,5α-

[1] For reduction of 5α- and 7α-bromocholestane-3β-ol-6-one acetates, D.J. James and C.W. Shoppee, J.Chem.Soc. 4224 (1954).

[2] H.B. Henbest, E.R.H. Jones, A.A. Wagland, and T.I. Wrigley, J.Chem.Soc. 2477 (1955).

[3] "Chemically pure" methanol sometimes contains enough heavy metals to catalyze debromination. Distillation of the solvents or addition of EDTA to the solution is effective to avoid debromination.



diol-6-one diacetate (III), which is not further reduced in the condition employed. The effects of lead and some other substances are summerized in Table 1.

Table 1

Substance added	Bromohydrin (II) (%)	Ketone (III) (%)
0.25 mg Pb as $Pb(OAc)_2$	0	100
0.25 mg Pb as $Pb(NO_3)_2$	0	100
0.04 mg Pb as $Pb(OAc)_2$	25	75
0.02 mg Pb as $Pb(OAc)_2$	60	40
0.01 mg Pb as $Pb(OAc)_2$	70	30
2.9 mg Sn as $SnCl_2$	70	30
0.25 mg Ba as $BaCl_2$	45	55
0.24 mg Ag as $AgNO_3$	45	55
0.26 mg Hg as $Hg(OAc)_2$	0	100
0.22 mg Ni as $Ni(OAc)_2$	0	100
0.20 mg Bi as BiO_3Na	70	30
0.20 mg Cu as $CuSO_4$	35	65
2.5 ml H_2O	100	0
2.0 mg $(C_6H_5COO)_2$	100	0
5.0 mg HCHO	100	0
5.0 mg $(CH_3)_2CO$	100	0
5.0 mg HCOOH	100	0

Condition - Sodium borohydride (0.20 g) is added to a solution of the bromoketone (0.20 g) and a given weight of metal salt (or other substance) in a mixture of methanol (20 ml) and dioxane (30 ml). After allowing to stand for 45 min at room temperature, the reaction mixture is acidified with

contd.

acetic acid and diluted with water (50 ml) to give precipitates that collected and dried. The composition of the mixture is calculated from special bands of its I.R. spectrum. Accuracy is about ± 3%.

The possibility of involving an intermediate bromohydrin (II) is excluded by the fact that the bromohydrin (II) is not dehydrobrominated to the ketone (III) in the reaction condition. The reaction rate of the bromoketone (I) with borohydride is not affected by the addition of lead acetate and is first order with respect to the bromoketone (I) in the presence of an excess borohydride. An existence of a common intermediate for both reactions is therefore suggested.

Tetrahedron Letters No. 15, pp. 516-522, 1961. Pergamon Press Ltd. Printed in Great Britain.

AN NMR STUDY OF ORIENTATION EFFECTS IN THE CATALYTIC DEUTERATION AND TRITIATION OF AROMATIC COMPOUNDS.[1] SIMPLIFICATION OF SPIN-COUPLED NMR SPECTRA BY THE METHOD OF MASSIVE DEUTERATION[2]

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A GENERAL procedure for the platinum-catalysed exchange of aromatic compounds with heavy water has already been reported.[3,4] The technique has been demonstrated to be a useful method for the synthesis of tritium labelled compounds when tritium oxide is used;[5] it possesses significant advantages over conventional techniques of recoil tritiation[6] and tritium gas irradiation.[7]

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[1] Part V of a series entitled "Deuterium Exchange Reactions, Reactions with Substituted Aromatics". (Part IV, see reference 4).

[2] Proton NMR Spectroscopy. XIII (Part XII, J.Phys.Chem. In press).

[3] W.G. Brown and J.L. Garnett, J.Amer.Chem.Soc. 80, 5272 (1958).

[4] J.L. Garnett and W.A. Sollich, Aust.J.Chem. In press.

[5] International Atomic Energy Agency Symposium, "The Detection and Use of Tritium in the Physical and Biological Sciences", Vienna, May 3-10, 1961.

[6] R. Wolfgang, F.S. Rowland and C.N. Turton, Science 121, 715 (1955).

[7] K.E. Wilzbach, J.Amer.Chem.Soc. 79, 1013 (1957).

The procedure involves a relatively simple one-step synthesis, the organic substrate need not be water soluble, no solvent is necessary, and a high level of tritium incorporation is achieved with most compounds when tritiated water of high specific activity is used. The labelled compound is obtained with a minimum of tritiated impurities, since by-product formation occurs only by catalytic means and not as a result of radiation-induced decompositions, etc., which often render difficult the radiochemical purification of the desired product.[8]

This catalytic method provides a source of labelled compounds which are difficult to obtain by other means. It also permits of simultaneous double-labelling when both deuterium and tritium are used in the exchange media; this is advantageous for isotopic distribution studies, since conventional tritiation procedures[6,7] yield only a tritiated product in which distribution must be evaluated by tedious chemical methods. When appreciable deuteration has occurred, a spectroscopic method may be used to determine isotopic distribution; for this purpose the proton NMR spectrum is particularly suitable at high deuterium contents, since the positions occupied by residual hydrogen are readily identifiable.

A typical example of the catalytic deuteration (or tritiation) procedure follows. Sodium benzoate (144 mg) was shaken in an evacuated sealed amoule with pre-reduced platinum oxide (12 mg) and 99.5% heavy water (500 mg) at 130°C for 10 hr. An 80 to 90% yield of benzoic acid containing 70 atom % D in the ring was obtained. A second sample, subjected to three consecutive treatments according to this procedure, contained over 90 atom % D in the ring.[9,10]

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[8] W.G. Brown and J.L. Garnett, Int.J.Appl.Rad.Isotopes 5, 114 (1959).

[9] Deuterium analyses were performed on a Metropolitan Vickers Type MS-2-G mass spectrometer, by the procedure of Graff and Rittenberg, Analyt.Chem. 24, 878 (1952).

[10] Tritiations have been conducted in an exactly similar manner. Tritium analyses were performed by the procedure of J.L. Garnett, W.K. Hannan and S.W. Law, Anal.Chim.Acta In press.

It is thus evident that highly deuterated compounds are readily produced by this technique. While many uses can be foreseen for such materials, it will suffice to introduce here a particular application to NMR spectroscopy, permitting the simplification and assignment of certain types of spectra which will later be used to determine the orientation effects in catalytic deuteration.

It is well-known that NMR is useful for the identification of positional isomers of aromatic compounds. However, in some cases (notably C_6H_5X and o-and m-C_6H_4XY) highly complex spectra are obtained, and the computations required for analysis are costly and time-consuming. The technique of "spin decoupling"[11] is generally inapplicable, owing to the small frequency difference between the interacting nuclei. We have therefore devised a new procedure for the simplification of spin-coupled NMR patterns which is based on random replacement of hydrogen atoms by deuterium to the level of ca. 75 to 95 atom % D. Under these conditions the residual hydrogen atoms will with high probability be spin-coupled only to deuterium atoms. The proton NMR spectrum thus will show only the much finer splittings characteristic of coupling to deuterium ($J_D/J_H = 0.1535$), with consequent minimization of second-order effects.

If it be necessary, the deuterium splittings may be wholly eliminated by means of H-D spin decoupling, thus providing perfectly sharp lines centered at the true shielding values.

This general method, termed "massive deuteration", is most satisfactory when all sites are equally deuterated (i.e. equilibrated) since then the areas of the separated NMR peaks will be proportional to the numbers of equivalent sites; for example, the peak due to para hydrogen in phenyl

[11] W.A. Anderson, Phys.Rev. 102, 151 (1956); J. Itoh and S. Sato, J.Phys. Soc.Japan 14, 851 (1959); R. Kaiser, Rev.Sci.Instrum. 31, 963 (1960).

derivatives is thus identified unambiguously. While any D-exchange method may be used, for example strong acid catalysis, the use of transition metal catalysts often permits of more facile equilibration and easier isolation of product.

The NMR spectrometer and techniques have been described.[12] However, owing to the relatively low hydrogen content of the samples, which is, of course, inherent in the method of massive deuteration, it is often desirable to use rather high sample concentrations, i.e. 6 to 10% (by volume or wt/vol) in CCl_4 or other solvent. Another difficulty stems from the electric quadrupole moment of deuterium, which causes the protons spin-coupled to it to give slightly broadened lines (ca. 2 c/s width at half-height); this effect too would be eliminated if H-D spin decoupling were employed. The τ-values[12] for several compounds which ordinarily exhibit rather complex spectra are listed in increasing order in Table 1. There is an evident

Table 1

Shielding Values[12] for Phenyl Derivatives as Determined by the Method of Massive Deuteration

Compound (10% wt/vol in CCl_4)	τ 2-H	τ 3-H	τ 4-H
Benzoyl chloride	1.90	2.50	2.39
Benzoic acid	1.88	2.57	2.48
Methyl benzoate	2.01	2.63	2.53
Fluorobenzene	3.01d	2.75d	2.91
Phenol	3.27	2.90	3.19
Aniline	3.49	2.97	3.35

correlation between shielding values and the electron-donating power of the substituent, and, as expected, the meta position is less sensitive than the para. However, no exact correspondence to Hammett's σ-values or to Taft's

[12] G.V.D. Tiers, J.Phys.Chem. 62, 1151 (1958); G.V.D. Tiers and F.A.Bovey, J.Phys.Chem. 63, 302 (1959).

inductive or resonance parameters is observed. This point will be dealt with in future publications.

For these measurements the 90% deuterated sample of benzoic acid, prepared above, was converted to the acyl chloride and the ester; the other compounds were deuterated to a similar level. In the case of fluorobenzene the o- and m-H absorptions were doublets because of spin coupling to the fluorine atom.

Once the assignment of NMR peaks to residual hydrogen at various positions has been made, it is a simple matter to determine the orientation by identifying the positions at which deuterium exchange is relatively slow. To do this it is only necessary to interrupt the exchange before complete equilibration has been achieved. Examples of orientation effects which have been observed for some of the compounds studied are listed in Table 2; further experiments are in progress. As contrasted with the reactivity at the ring, it is significant that the non-aromatic hydrogens in methyl benzoate, anisole, stilbene, and trans-cinnamic acid do not undergo appreciable exchange. However, the aliphatic hydrogens of bibenzyl are deuterated readily, and it had previously been found that the methyl hydrogens of toluene are very active toward exchange when treated with Raney nickel plus D_2O.[13]

Such observations are of importance in studies of the mechanism of transition-metal catalysis. The term "charge-transfer no-bond adsorption" has been used[14] to describe chemisorption[15] of aromatic compounds; to explain the relative reactivities of various aromatics, it has been postulated that chemisorption involves π-electron delocalization.[14] For example

[13] G.V.D. Tiers, Ph.D. Dissertation, The University of Chicago, 1956, pp. 121-132.

[14] Presented at the May 1960 meeting of the University of New South Wales Chemical Society and subsequently published in Proc.Royal Aust.Chem.Inst. In press.

[15] F.A. Matsen, A.C. Makrides and N. Hackerman, J.Chem.Phys. 22, 1800 (1954).

Table 2

Orientation Effects in Catalytic Deuteration

Compound	Atom % D in ring[a]	Position[b]	Atom % D[c]
Sodium benzoate	90	ortho	90 ± 2
		m + p	90 ± 2
Sodium benzoate	70	ortho	57 ± 2
		m + p	79 ± 1
Sodium benzoate	61	ortho	26 ± 1
		m + p	84 ± 1
Phenol	52	meta	63 ± 1
		o + p	45 ± 1
Pyridine	35	α	53 ± 2
		β + γ	23 ± 1

[a] The extent of deuteration was carried to 65-85% of the limiting value in all cases except the first, in which near-equilibration was achieved by three successive treatments. Analyses for total ring D done according to reference 9.

[b] When two peaks are not adequately resolved for separate integration, the combined value is given.

[c] Amounts of deuterium were obtained by difference from the amount of residual hydrogen determined by means of an electronic integrator built according to plans furnished by Varian Associates.

pyridine may be chemisorbed by its lone-pair or by the π-electrons; while the results of Table 2 indicate a definitely greater reactivity at the α-position, this is by no means as large as might have been expected if lone-pair adsorption were dominant.[16]

The results of Table 2 are indicative of orientation, but to deduce true relative rates from such measurements would require additional data, e.g. exact values for equilibrium deuterium content, etc.[13] Work of this nature is in progress.

Acknowledgements - The authors are indebted to Lt.-Commander J. Mason

[16] W.M. Lauer and L.A. Errede, J.Amer.Chem.Soc. 76, 5162 (1954).

for assistance with mass spectrometer analyses, and to R.P. Dickey for improvements in the design of the NMR electronic integrator and for its operation. The research group at the University of New South Wales gratefully acknowledges financial support from the New South Wales State Cancer Council and the Australian Institute of Nuclear Science and Engineering.

1961

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THE NEOPHYL CARBENE REARRANGEMENT

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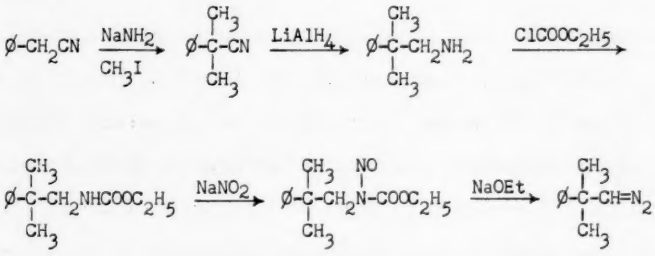
(Received 26 July 1961)

IN view of the extensive studies that have been made of rearrangements in the neophyl (2-methyl-2-phenylpropyl) system which proceed via carbonium ion[1] or radical[2] intermediates it was of interest to study rearrangements in this system which proceed via a carbene intermediate. Therefore, the thermal decomposition in an aprotic solvent of 1-diazo-2-methyl-2-phenylpropane, henceforth referred to as the neophyl diazo compound, was investigated. This work represents a preliminary study in the investigation of migration aptitudes in carbene rearrangements.

The neophyl diazo compound, I, was prepared by the following sequence of reactions;



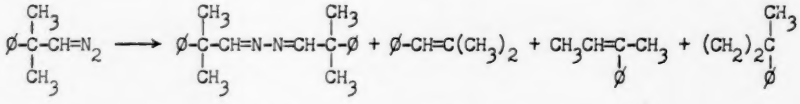
I

[1a] S. Winstein, B.K. Morse, E. Grunwald, D.C. Schreiber and J. Corse, J.Amer.Chem.Soc. 74, 1113 (1952); [b]S. Winstein and A.H. Fainberg, Ibid. 79, 1608 (1957); [c]R. Heck and S. Winstein, Ibid. 79, 3432 (1957); [d]W.H. Saunders and R.H. Paine, Ibid. 83, 882 (1961).

All compounds in this series were characterized. The presence and concentration of the neophyl diazo compound, I, was verified by its reaction with benzoic acid and subsequent identification of the resulting neophyl benzoate.

The thermal decomposition of the neophyl diazo compound, 0.1 molar in hexane, at 59°C over a period of 96 hr was observed. Results of two typical runs in this series are indicated in Table 1.

Table 1



I II III IV V

Run[c]	mmoles I	% N_2	% II[a]	Total % hydrocarbon	% III[b]	% IV[b]	% V[b]
12	86	75	54	35	49	8.5	43
15	85	70	45	36	51	9.0	40

[a] Found: C, 81.95; H, 8.08. Calc. for $C_{20}H_{24}N_2$: C, 82.14; H, 8.27.
[b] Expressed as percentage of total hydrocarbons.
[c] Total number of runs investigated was 15.

The hydrocarbons were isolated by distillation under reduced pressure. The possibility of double bond migration in III and IV, as well as stereo isomeric forms of IV rendered the resolution of this mixture difficult. Indeed the infrared spectra indicated the presence of terminal olefin. By hydrogenation of the mixture and subsequent analytical scale gas chromatography the percentage of 1-methyl-1-phenylcyclopropane, V, and an unresolved mixture of iso- and sec-butylbenzene were determined. The mixture of iso-

[2a] W.H. Urry and M.S. Kharasch, J.Amer.Chem.Soc. 66, 1438 (1944); [b]S. Winstein and F.H. Seubold, Ibid. 69, 2916 (1947); [c]W.H. Urry and N. Nicolaides, Ibid. 74, 5163 (1952); [d]F.H. Seubold, Ibid. 75, 2532 (1953).

and sec-butylbenzene was isolated by preparative scale VPC and determined by comparison of its infrared spectrum with that of mixtures of the authentic hydrocarbons. The percentage composition of the isolated mixture of iso- and sec-butylbenzene was further verified by a differential infrared spectrum and the near identity of its index of refraction with that of the mixture of authentic hydrocarbons. A differential infrared spectrum of the complete hydrogenated mixture further substantiated the percentage of 1-methyl-1-phenylcyclopropane.

The most interesting aspect of these results is that the phenyl/methyl migration aptitude in this rearrangement is about 10:1. This can be contrasted with the lack of methyl migration in radical rearrangements[2,3] and the 3000-300:1 phenyl/methyl migration aptitudes characteristic of normal carbonium ion rearrangements.[1d] This result is consistent with the postulate that the carbenic intermediate is a highly reactive electrophilic species.[4] Although the agreement is fortuitous, it is of interest to note that Curtin[5] stated that 10 is a conservative estimate for the phenyl/methyl migration ratio in the deamination of 1-amino-2-phenylpropanol-2, a rearrangement of the type postulated to proceed via the very reactive "Hot" carbonium ion.[6]

Another interesting aspect of these results is the 1.2 ratio of phenyl migration to insertion product. A great predominance, as high as 19:1, of hydrogen migration to insertion product from a variety of systems has been noted by other workers.[7] From these results a tentative order of migration

[3] M.A. Muhs, Diss.Abstr. 14, 765 (1954).

[4] R.C. Woodworth and P.S. Skell, J.Amer.Chem.Soc. 81, 3383 (1959).

[5] D.Y. Curtin and S. Schmukler, J.Amer.Chem.Soc. 77, 1107 (1955).

[6] J.D. Roberts, C.C. Lee, W.H. Sounders Jr., J.Amer.Chem.Soc. 76, 4501 (1954). A. Streitwieser Jr., J.Org.Chem. 22, 861 (1957). D.J. Cram and J.E. McCarty, J.Amer.Chem.Soc. 79, 2866 (1957).

[7] L. Friedman and H. Shechter, J.Amer.Chem.Soc. 81, 5512 (1959); Ibid. 82, 1002 (1960); L. Friedman and J. Berger, Ibid. 83, 501 (1961). G.L. Closs, Abstracts of Papers presented at the 138th Meeting of the Amer.Chem.Soc., September, 1960, New York, p. 9-P.

aptitudes, hydrogen phenyl methyl, might be postulated for carbene rearrangements. This order is not inconsistent with that observed in rearrangements that proceed via carbonium ions.[8]

The authors wish to express their appreciation to Dr. J.W. Wilt of Loyola University for his helpful discussions of this problem. The preliminary observation of this rearrangement was made during work on another problem supported by the Research Corporation. The present investigation is supported by the National Science Foundation.

[8] C.K. Ingold, Structure and Mechanism in Organic Chemistry pp. 475-477. Cornell University Press, Ithaca (1953).

Tetrahedron Letters No. 15, pp. 527-529, 1961. Pergamon Press Ltd. Printed in Great Britain.

HETEROLYTIC ISOMERIZATION OF SOME ACYL-SULPHONYL PEROXIDES

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(Received 28 July 1961)

In the study of the thermal decomposition of new peroxides such as $AlkSO_2O\text{-}OCOC_6H_5$, heterolytic isomerization to the mixed anhydride of the alkane sulphonic acid and phenoxyformic acid was observed. Such a decomposition process for acyl-sulphonyl peroxides has not been noted until recently. The data obtained showed that the isomerization is catalysed by the alkanesulphonic acid formed by the homolytic decomposition of the peroxide, and does not depend on the solvent polarity. The phenomenon differs from the known heterolytic isomerization of 4-methoxy-4'-nitro-benzoyl peroxide which preceeds only in polar solvents.[1]

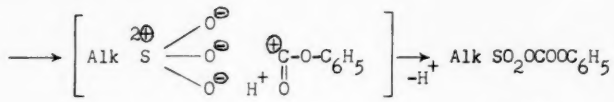
Decomposition of peroxide where Alk=CH_3-(I) and C_2H_5-(II) yielded 83%* of the mixed anhydride in benzene, 80% in isopropyl alcohol, and 45% in carbon tetrachloride.

The following scheme is suggested for formation of the mixed anhydride (V):

III

* Per mole of decomposed peroxide.

[1] J.E. Leffler, J.Amer.Chem.Soc. 72, 67 (1950).



IV V (1)

Initial proton addition results in a heterolytic degradation to give the sulphonic acid anion and the benzoyloxy-cation (III). The latter rearranges into the carbonium cation (IV) (rearrangement being facilitated by the availability of the electron-donating phenyl group). Mixed anhydride formation (V) then takes place by proton loss.

To verify this suggestion, the peroxide was decomposed in isopropyl alcohol in the presence of dry finely divided potash. In the solvent distillate 75% of acetone was found, in comparison to 17% in the absence of potash. Alternatively, when sulphonic acid is introduced into the peroxide solution in carbon tetrachloride, the reaction can be substantially affected. Thus, up to 65% of mixed anhydride was found as compared to 45% in the absence of the sulphonic acid. At the same time it was shown that aprotonic acids ($AlCl_3$, $SnCl_4$ and $SbCl_5$) in the amount of 5% M also favour heterolytic isomerization of the peroxides. Up to 85% of the mixed anhydride was isolated. The explanation of the activating effect of aprotonic acids lies in the ability of the latter to complete their valency shells by co-ordination with the sulphonic acid anion. In this case the benzoyloxy-cation is also formed.

In the presence of potash, sulphonic acids, and aprotonic acids a considerable acceleration of peroxide decomposition was observed.

The mixed anhydride of methane-sulphonic acid and phenoxyformic acid was separated by vacuum distillation of the reaction mixture resulting from the decomposition of peroxide (I) in benzene.

The α-naphthyl urethane, m.p. 133-133.5°, was obtained by reaction of the anhydride with α-naphthyl amine. A mixture with a sample of the urethane derived from α-naphthylisocyanate and phenol melted without depression. A similar anhydride was obtained from the silver salt of methane-sulphonic acid and phenylchloroformate. B.p. 144/4 mm Hg.

n_D^{20} - 1.5106; d_4^{20} - 1.3400. Calc. MR - 48.45; Found MR - 48.25.

For $C_8H_8O_5S$: Calc. % C-44.50, H - 3.70, S-14.80, M - 216. Found % C - 44.38, H - 3.79, S - 14.37, M - 214.5 - cryoscopically in benzene.

The mixed anhydrides proved to be active acylating agents of substances having labile hydrogen atoms.

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QUINONE DEHYDROGENATION - A GENERAL METHOD OF PREPARATION OF ORGANIC CATIONS

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(Received 17 July 1961)

EVIDENCE has been presented[1] that the dehydrogenation of hydroaromatic compounds by quinones proceeds as a two-stage ionic process. In the first and the rate-determining step abstraction of hydrogen occurs as hydride ion, and is followed by the rapid transfer of a proton from the resulting conjugate acid of the substrate to the quinol anion:

$$RH_2 + Q \rightarrow RH^+ + QH^- \quad (1)$$

$$RH^+ + QH^- \rightarrow R + QH_2 \quad (2)$$

However, step (1) may itself represent a summary of two successive reactions:

$$RH_2 + Q \rightarrow RH^\bullet + QH^\bullet \quad (1a)$$

$$RH^\bullet + QH^\bullet \rightarrow RH^+ + QH^- \quad (1b)$$

In the case where $RH^\bullet$ is a stable, long-lived radical, it is likely that reaction (1a) would be followed by

$$RH_2 + QH^\bullet \rightarrow RH^\bullet + QH_2 \quad (3)$$

[1] E.A. Braude, L.M. Jackman and R.P. Linstead, J.Chem.Soc. 3548, 3564 (1954); J.R. Barnard and L.M. Jackman, J.Chem.Soc. 3110 (1960); E.A. Braude, L.M. Jackman, R.P. Linstead and J.S. Shannon, J.Chem.Soc. 3116 (1960).

Alternatively, steps (1a) and (3) might merge into a single process:

$$2RH_2 + Q \rightarrow 2RH^{\bullet} + QH_2 \qquad (4)$$

It seemed that by the use of structurally suitable substrates it might be possible to isolate stable cations (RH^+) or radicals ($RH^{\bullet}$) in quinone dehydrogenations. Isolated instances[2] appear in the literature of the formation of heterocyclic quaternary ammonium salts by the action of quinones on heterocyclic hydroaromatic compounds. Overall loss of hydrogen as hydride ion must occur in these cases. We now describe the use of quinones in a novel general method of preparation of stable hydrocarbon cations, in a systematic application to the preparation of heterocyclic salts, and, in specific instances, for the preparation of stable radicals.

In reactions involving hydride abstraction the dehydrogenative efficiency of quinones was found to increase with increasing redox potential. The following quinones proved to be the most useful (abbreviated names henceforth used are in brackets): tetrachloro-1,2-benzoquinone (T.B.Q.), $E^{\circ} = 0.87v$; 2,3-dichloro-5,6-dicyano-1,4-benzoquinone (D.D.Q.), $E^{\circ} \simeq 1.0v$; and chloranil, $E^{\circ} = 0.71v$. The first of these possesses distinct practical advantages over the other two, chiefly owing to its ready solubility in acetic acid, the preferred reaction solvent, and to the high solubility of the corresponding quinol in ether. Using these quinones, members of the following classes of organic salts were readily prepared.

Tropylium salts

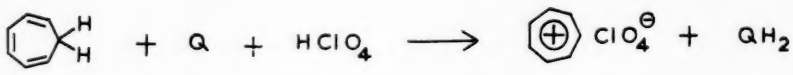
Cycloheptatriene reacted instantly with D.D.Q., best in methylene chloride, to give a complex* (91%),** black needles from crimson solutions in acetonitrile, m.p. 177-178° (decomp.), which is provisionally formulated

* Compounds whose names are underlined are new.

** Yields in brackets.

2 D. Buckley, S. Dunstan and H.B. Henbest, J.Chem.Soc. 4883 (1957).

as tropylium 2,3-dichloro-5,6-dicyano-1,4-quinolate. The fine structure of this complex, and that from 1,2,3-triphenylcyclopropene with D.D.Q. (see below), is under investigation. In contrast, cycloheptatriene reacted immediately with D.D.Q. and 70% (w/w) perchloric acid in cold acetic acid to give tropylium perchlorate (92%), colourless fern-shaped crystals which become translucent $> 275^{\circ}$ and decompose with bubbling $> 285^{\circ}$, also produced (90%) by the action of perchloric acid in acetic acid on the complex. Replacement of D.D.Q. by the following quinones also gave tropylium perchlorate: T.B.Q. (97%); chloranil (70%); and 1,4-benzoquinone (30%).



The following salts were similarly prepared from cycloheptatriene or the cycloheptatriene - D.D.Q. complex in acetic acid, using the reagents indicated: tropylium picrate, D.D.Q. and picric acid (51%), yellow needles, m.p. 120-125° (decomp.);[3] tropylium tetroxalate, T.B.Q. and oxalic acid dihydrate (83%), colourless spears, m.p. 140-145° (decomp.) with darkening $> 130^{\circ}$; ditropylium iodide-triiodide, complex and sodium iodide (79%), dark brown needles, m.p. 128.5-129.5°; tropylium iodide,[4,5] T.B.Q. and sodium iodide (75%), or by the action of acetone on tropylium iodide-triiodide (54%), scarlet needles, m.p. 132-133°;[6] tropylium triiodide, (along with tropylium iodide) by the action of acetone on tropylium iodide-

[3] M.J.S. Dewar and R. Pettit, J.Chem.Soc. 2026 (1956), give m.p. 114-115°.

[4] H.J. Dauben, F.A. Gadecki, K.M. Harmon and D.L. Pearson, J.Amer. Chem.Soc. 79, 4557 (1957).

[5] M.J.S. Dewar and R. Pettit, J.Chem.Soc. 2021 (1956).

[6] Reported m.p.s. 127° [4] and 117°.[5]

triiodide (58%), garnet-red needles, m.p. 132-133°;[7] tropylium bromide,[4,5,8] complex and lithium bromide (12%), yellow crystals, m.p. 198-204° (decomp.);[9] tropylium hydrogen sulphate, complex and sulphuric acid (low yield), colourless needles, decomp. > 175°; tropylium toluene-p-sulphonate, complex and toluene-p-sulphonic acid (55%), pale buff plates, m.p. 125-130° (decomp.); tropylium pyrophosphate (?), D.D.Q. and 90% orthophosphoric acid (55%), colourless plates, m.p. 125-129° (decomp.).

Cyclopropenylium salts

1,2,3-Triphenylcyclopropene with D.D.Q. in methylene chloride gave a complex (79%), purple needles from crimson solutions, m.p. 179-181° (decomp.). However, addition of perchloric acid to a hot solution of 1,2,3-triphenylcyclopropene and D.D.Q. in acetic acid gave triphenylcyclopropenylium perchlorate (95%), colourless needles, m.p. 229-231° (decomp.), also prepared by the action of perchloric acid on the complex. Similar conditions were employed for the preparation of the following salts from 1,2,3-triphenylcyclopropene, using the reagents specified: triphenylcyclopropenylium picrate, D.D.Q. and picric acid (88%), yellow needles, m.p. 193-197°;[10] triphenylcyclopropenylium iodide complex and sodium iodide (80%), yellow needles, m.p. 221-224°.

Perinaphthenylium salts

The product obtained by the action of quinones on perinaphthene depends on the presence or absence of a strong acid (see also below). Perinaphthene, chloranil, and perchloric acid in cold acetic acid gave perinaphthenylium perchlorate (75%),[11,12] yellow needles which decompose slowly on being heated,

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[7] Reported m.p. 127°.[4]

[8] W.E. Doering and L.H. Knox, J.Amer.Chem.Soc. 76, 3203 (1954).

[9] Reported m.p. 203°.[4,5,8]

[10] R. Breslow and C. Yuan, J.Amer.Chem.Soc. 80, 5991 (1958), give m.p. 194-197° (decomp.).

[11] W. Bonthrone and D.H. Reid, J.Chem.Soc. 2773, (1959).

[12] R. Pettit, J.Amer.Chem.Soc. 82, 1972 (1960); Chem. & Ind. 1306 (1956).

also produced (81%) using 1,4-benzoquinone in place of chloranil. Addition of 3,6,9-trimethylperinaphthan-1-ol to a boiling solution of T.B.Q. and perchloric acid in acetic acid gave directly 1,4,7-trimethylperinaphthenylium perchlorate[11] (89%), dehydration to 3,6,9-trimethylperinaphthene occurring in situ, copper coloured needles which decompose $> 240^{\circ}$.

Heterocyclic salts

The wide preparative possibilities in heterocyclic chemistry are illustrated by the preparation of the following salts in acetic acid containing perchloric acid: thiaxanthylium perchlorate,[13] chloranil and thiaxanthene (87%), scarlet prisms, m.p. 216-218°; 5-methylphenanthridinium perchlorate, chloranil and 5-methyl-5,6-dihydrophenanthridine (94%), colourless needles, m.p. 192-195°; 3-(1,2-dimethylindolizin-3-yl)methylene-1,2-dimethylindolizinium perchlorate, chloranil and di-(1,2-dimethylindolizin-3-yl)methane (10%), greenish-black rosettes of needles, decomp. $> 261^{\circ}$; 1-thioxonianaphthalene perchlorate,[13,14] T.B.Q. and 1-thiachroman-4-ol (92%), greenish-yellow needles which melt (decomp.) on a block preheated to 221°. With D.D.Q. alone in acetic acid 9,10-dihydroacridine gave acridinium 2,3-dichloro-5,6-dicyano-1,4-quinolate (93%), orange needles from acetonitrile, m.p. 220.5-222.5° with resolidification to yellow crystals which decompose slowly with partial melting on being further heated.

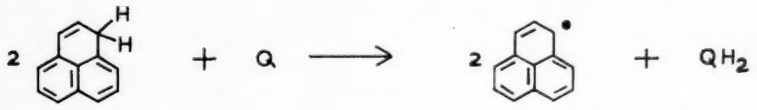
Radicals

In contrast to its behaviour in the presence of strong acids, perinaphthene reacted at room temperature with many quinones (D.D.Q., chloranil, T.B.Q., 1,4-benzoquinone, 1,2- and 1,4-naphthaquinone) in both polar and non-polar solvents (benzene, methylene chloride, carbon tetrachloride, acetonitrile, nitromethane) to give the perinaphthyl radical.[15]

[13] W.Bonthrone and D.H. Reid, Chem. & Ind. 1192 (1960).

[14] A. Lüttringhaus and N. Engelbert, Chem.Ber. 93, 1525 (1960).

[15] D.H. Reid, Chem. & Ind. 1504 (1956); Tetrahedron 3, 339 (1958).



The results reported demonstrate that quinones can dehydrogenate both by a hydrogen atom and by an overall hydride-transfer mechanism.

We hope to study the reactions of quinones, along these lines, with hydrocarbon complexes of the transition metals and related compounds, e.g. the cycloheptatriene-metal carbonyls.

Full details of these and related experiments will be published later.

Thanks are expressed to the Carnegie Trust for the Universities of Scotland for a Research Grant (B.B.M.), the Department of Scientific and Industrial Research for Research Studentships (M.F., H.A.S.P. and R.G.S.), the Royal Society for a Research Grant, and Messrs. J. Bayne and B.L. Thomas for the preparation of intermediates.

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STRUCTURE OF FLAVENSOMYCINIC ACID

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(Received 22 June 1961; in revised form 1 September 1961)

FLAVENSOMYCIN is a new substance having antibiotic and anti-fungin properties, recently isolated by Giolitti and co-workers.[1,2]

The methanolysis of flavensomycin carried out in the presence of Dowex 50-X8 ion-exchange resin, gave a mixture of products from which a crystalline compound was isolated (pale-yellow needles, m.p.232-233°). This compound was assigned the empirical formula $C_{10}H_{11}NO_5$; owing to its acidic properties we called it "flavensomycinic acid" (I).

The flavensomycinic acid is an optically inactive strong acid, which gives negative ninhydrin, Ehrlich, triphenyl-tetrazolium chloride tests; it gives a red-violet colour with ferric chloride and the hydroxamic acid test[3] is positive under the conditions specific for esters and lactones.

The acid (I) contains a α-β unsaturated carbomethoxy group [I.R.: 1724 cm^{-1} (Nujol)]: by mild alkaline hydrolysis a crystalline dibasic acid (II) was obtained; II, called by us flavensomycinoic acid, by esterification with methanol in the presence of Dowex 50 resin reforms the acid (I). Methylglyoxylate (III) was obtained by ozone-oxidation of the sodium salt

[1] R. Craveri and G. Giolitti, Nature, Lond. 179, 1307 (1957).

[2] R. Craveri, A. Lugli and G. Giolitti, Nuovi Ann. d'Igiene e Microb. IX (2), 185 (1958).

[3] A.I. Vogel, Practical Organic Chemistry (3rd Ed.) p.1063. (1956).

of I in water and by catalytic hydrogenation the acid (I) yields a dihydroflavensomycinic acid (IV) [I.R.: 1736 cm^{-1} (saturated ester)] for which both the hydroxamic acid and the ferric chloride tests were positive.

The I.R. spectrum of I has bands at 1295, 1172, 993, 763, 666 cm^{-1} typical of the fumaric acid derivatives[4]; the acid or alkaline hydrolysis of I and IV under drastic conditions yields respectively fumaric and succinic acid.

The nitrogen atom of I was ascribed to a secondary amidic group. The I.R. spectrum of I shows absorption maxima at 3200 cm^{-1} (-NH- stretching), at 1613 and 1563 cm^{-1} (secondary amide I and II band) which are shifted respectively to 3400, 1631, 1536 cm^{-1} in the spectrum of IV in chloroform.

The acid (I) reacts rapidly in the cold with chromic acid in acetic solution; from the reaction mixture was isolated the fumaramic acid methylester (V): this fact can only be explained if the amidic nitrogen of I is bound to a carbon atom which is easily oxidized to a carboxyl group.

The flavensomycinic acid (I) contains a methyl group bound to carbon; the above facts are consistent with the partial formulation of I as (A):

$$C_4H_2O_2 \longrightarrow \begin{cases} -NH-CO-\overset{H}{\underset{|}{C}}=\overset{|}{\underset{H}{C}}-COOCH_3 \\ -(C)-CH_3 \end{cases}$$

A

The two oxygen atoms of the $C_4H_2O_2$- moiety are ascribable to a β-dicarbonyl structure, which would account for the enolic and acidic properties of the flavensomycinic acid and of its dihydroderivative. The acids I and IV react with the usual carbonyl reagents; however no definite product could be identified from the last reaction owing to the small available amounts of flavensomycin.

[4] W.L. Walton and R.B. Hughes, Analyt. Chem. 28, 1388 (1956).

The U.V. spectrum of the dihydroacid IV shows a maximum at 259 mμ; the absorption curve is very similar to those of the enolized "trans-fixed" β-diketones.[5] It follows from the above facts and considerations that the β-diketone group should belong to a cyclic system with four carbon atoms.

The characteristic properties of the 1,3-cyclobutanedione derivatives as described by Woodward[6] are in perfect agreement with those of I and its derivatives; the most remarkable property is their powerful acidity. By potentiometric titration it is possible to determine for the flavensomycinoic acid (II) the pK'_{a_1} 3.5 and pK'_{a_2} 4.7. The dihydroflavensomycinoic acid (VI) obtained in solution by catalytic hydrogenation of II in water had pK'_{a_1} 2.8 and pK'_{a_2} 3.6. The pK'_{a_1} 3.5 of II and pK'_{a_1} 2.8 of VI could be ascribed to the enol dissociation.

The strong acidity of I and IV is further showed by their spectroscopic behaviour in the U.V. The acid (I) has two absorption maxima in methanol at 330 mμ (log ε 3.92) and at 259 mμ (log ε 4.38); the former disappears in the spectrum of its dihydro-derivative, while the latter remains unchanged ($\lambda_{max}^{CH_3OH}$ 259 mμ; log ε 4.36). The U.V. spectrum of IV is substantially the same in alkaline solution; in acid solution the maximum shows a mild hypsochromic effect (λ_{max} 252 mμ), a lower molecular extinction coefficient (log ε 3.95) and a considerable shoulder appears at 259 mμ (log ε 3.92). It is clear that in diluted methanol solution the acid IV is completely dissociated and that the anion is present in a considerable amount even in acid solution.

By methylation with diazomethane the dihydroflavensomycinic acid gives

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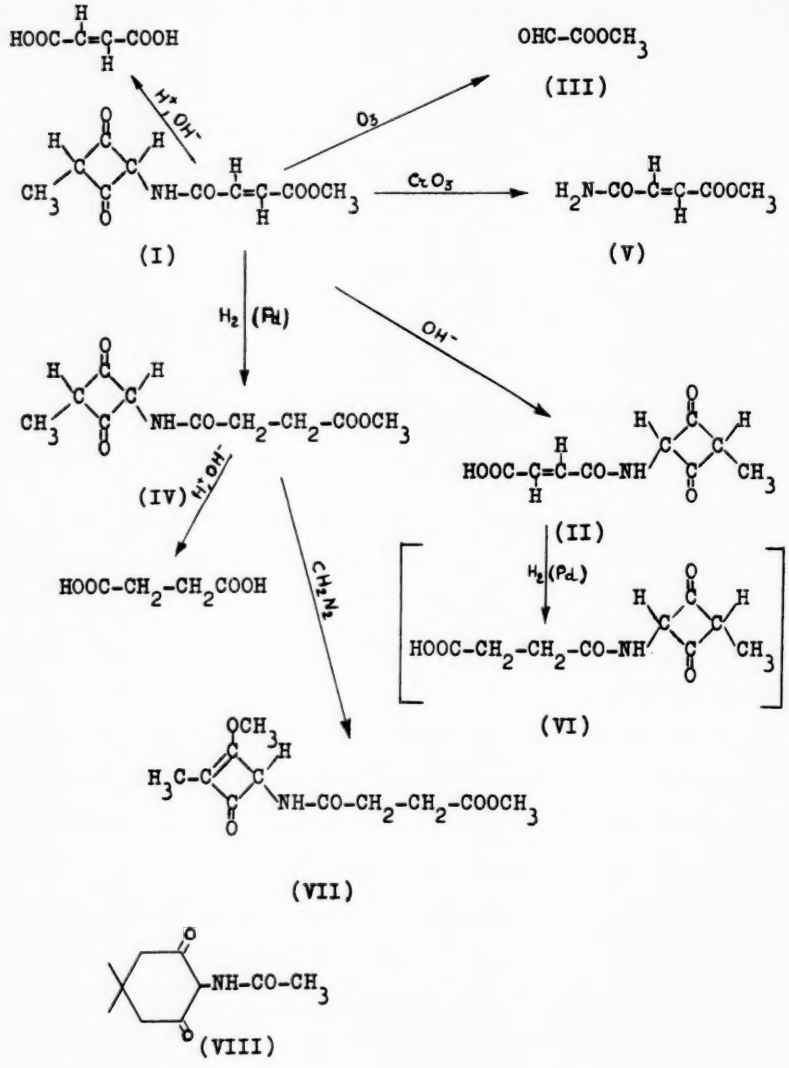
[5] R.B. Woodward and E.R. Blout, J.Amer.Chem.Soc. 65, 562 (1943); E.R. Blout, V.W. Eager and D.C. Silverman, Ibid. 68, 566 (1946); B. Eistert and W. Reiss, Chem.Ber. 87, 108 (1954).

[6] R.B. Woodward and G. Small, Jr., J.Amer.Chem.Soc. 72, 1297 (1950).



a neutral methylether (VII) [white needles, m.p.117-118°. I.R.: 1739 cm^{-1} (saturated ester), 1692 cm^{-1} (α-β unsaturated ketone), 1258 cm^{-1} (vinylic

ether[7])] which has negative reaction with ferric chloride and is very readily hydrolysed to the dihydroacid (IV).

The U.V. spectrum of VII shows an absorption maximum at 249 mμ[8] with a hypsochromic effect of 10 mμ ($\lambda^{\beta\text{-diket. in alk. media}}_{max} - \lambda^{enolether}_{max}$) with respect to the anion of IV; this shift is of the same order of magnitude as that observed for 1,3-cyclobutandiones.

The behaviour of IV to reduction is also typical for 1,3-cyclobutandione structure. In fact IV, unlike larger cyclodiones,[9] is not hydrogenated in the presence of catalyst and is not reduced by $NaBH_4$ while the acyclic β-diketones are.[10]

In agreement with the behaviour of cyclo β-diketones,[11] IV is oxidized rapidly by sodium periodate in neutral solution at 0°: oxalic and succinamic acids are obtained through a mechanism similar to that reported by Wolfrom and Huebner (loc.cit.).

Besides, by treatment with an excess of bromine in CCl_4, IV gives a monobromoderivative, which reduces triphenyltetrazolium chloride in the cold as common to α-halogenoketones.

By strong alkaline hydrolysis the β-diketone system of IV is cleaved. The mixture of cleavage products, unlike IV, reduces triphenyltetrazolium chloride and by oxidation with H_2O_2 in alkaline solution gives succinic and propionic acids.

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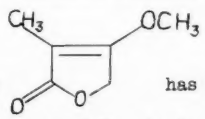
[7] The tetrinic acid methyl ether  has a band at 1259 cm^{-1} (unpublished observation from our own laboratories).

[8] The 1,1-diphenyl-2-ethoxy-3-methylcyclobut-2-ene-4-one has a maximum at 248 mμ [J.Nieuwenhuis and J.F. Arens, Rec.Trav.Chim. 77, 1153 (1958)]. The 1,3-dipentyl-2-ethoxycyclobut-en-4-one has a maximum at 245 mμ [J. Nieuwenhuis and J.F. Arens, Rec.Trav.Chim. 77, 761 (1958)].

[9] J.P. Wibaut and H.P.L. Gitsels, Rec.Trav.Chim. 60, 577 (1941).

[10] J. Dale, J.Chem.Soc. 910 (1961).

[11] M.L. Wolfrom and J.M. Bobbitt, J.Amer.Chem.Soc. 78, 2489 (1956): C.F. Huebner, S.R. Ames and E.C. Bubl, Ibid. 68, 1621 (1946).

Further information on the structure of flavensomycinic acid is obtained from comparison of the I.R. spectra of I and IV with that of 2-acetylamino-dimedone (VIII).[12] The spectrum in Nujol of the latter compound shows a very broad band at 2632 cm^{-1} (chelated OH) while it has no absorption in the region 1700 cm^{-1} (the keto form of dimedone absorbs at 1702 cm^{-1} [13]). The band of amidic -C=O of VIII masks nearly completely the band indicative of the "conjugated chelate" type of enolization which would fall in the same region. The spectrum of IV, very similar to that of VIII, has at 2632 cm^{-1} the very broad band of chelated OH, while it does not have any absorption in the regions corresponding to the keto and the α-β unsaturated form (this latter should fall at 1692 cm^{-1}, as shown by the spectrum of VII). It follows that the dihydroflavensomycinic acid (IV) in the solid state is in the "enol conjugated chelate" form, unlike the dimethylcyclobutandione.[14] The spectrum of I in Nujol has a broad absorption at 2632 cm^{-1} and a band of medium intensity at 1692 cm^{-1}, which can be probably ascribed to the α-β unsaturated keton group. Besides, a band is present at 917 cm^{-1} which, according to Reid (loc.cit.), is typical skeletal vibration of cyclobutanes.

The NMR spectrum of the enolether VII[15] shows that it contains fifteen protons: one in N-H (elongated signal at 460 cps), three in $-COOCH_3$ (signal at 219 cps, three in $H_3C-O-C=C-$ (signal at 242 cps), three in $H_3C-C=C-$ (signal at 158 cps) and five protons in the neighbourhood of 158 cps ascribable to the system A_2B_2 of the $-N-CO-CH_2-CH_2-CO-$ group and to the residual

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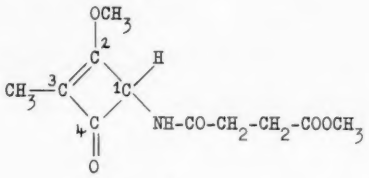
[12] Unpublished from our own laboratories.

[13] R.S. Rasmussen, D.D. Tunnicliff and R.R. Brattain, J.Amer.Chem.Soc. 71, 1068 (1949).

[14] E.B. Reid and S.J. Groszos, J.Amer.Chem.Soc. 75, 1655 (1953).

[15] We are greatly indebted to Dr. A. Melera for the measurement of the NMR spectra. Measurements were carried out on a Varian 4302, 60 megacycles spectrophotomer with electronic integrator, in the Research Laboratory of the Varian A.G., Zürich. Sample was dissolved in $CDCl_3$ and TMS was used as internal reference.

proton bound to the cyclobutane ring. This spectrum proves that the enolic double bond is in 2-3 (3-4), as in (B)



B

Acknowledgement - We are greatly indebted to Prof. G. Giolitti for providing the flavensomycin and to Dr. G. Ricca for discussions about the I.R. spectra.

Tetrahedron Letters No. 16, pp. 544-553, 1961. Pergamon Press Ltd. Printed in Great Britain.

A POSSIBLE BIOSYNTHETIC RELATIONSHIP BETWEEN THE CYCLOPENTANOID MONOTERPENES AND THE INDOLE ALKALOIDS

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The Squibb Institute for Medical Research, New Brunswick, N.J.

(Received 18 August 1961)

IN the well-known Barger-Hahn hypothesis[1,2] the carbon skeleton of yohimbine (I), is considered to be derived from tryptamine, phenylalanine and formaldehyde or its C_1 equivalent. This proposal later gained considerable support as a consequence of the attractive suggestion of Woodward,[3] that a related pathway involving the fission of a 3,4-dihydroxyphenylalanine-derived ring E with the incorporation of a single acetate unit, could simply explain the origin of strychnine. A most valuable consequence of this novel postulate has been the successful biosynthetic anticipation of the subsequently determined structures of a number of other indole alkaloids of varying degrees of complexity, e.g. corynantheine (II)[4] and echitamine (III),[5] and also the isoquinoline base, emetine (IV).[6]

Although in relation to the indole alkaloids the utilization of a tryptamine unit is almost self-evident and has indeed recently been demonstrated

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1 G. Barger and C. Scholz, Helv.Chim.Acta 16, 1343 (1933).

2 G. Hahn and H. Werner, Liebigs Ann. 520, 123 (1935).

3 R.B. Woodward, Nature, Lond. 162, 155 (1948).

4 M.M. Janot, R. Goutarel and V. Prelog, Helv.Chim.Acta 34, 1207 (1951).

5 Miss J.A. Hamilton, T.A. Hamor, J. Monteath Robertson and G.A. Sim, Proc.Chem.Soc. 63 (1961).

6 Sir Robert Robinson, Nature, Lond. 162, 524 (1948).

by the incorporation of tryptophan-2-^{14}C into ajmaline (V),[7] even in the relatively straightforward application of the Barger-Hahn scheme to yohimbine, the details of the required modifications of the phenylalanine precursor are less clear. The ability of C_1 units to substitute into the tyrosine nucleus has been established in the Streptomyces antibiotic novobiocin,[8] however, in this instance substitution occurs at the position meta to the original carbon side chain. The difficulty in adequately explaining the position of the yohimbine carbomethoxy group has been stressed by Robinson[9], who proposed a mechanism involving the expansion of ring E to a tropolone intermediate, with subsequent extrusion of the carboxyl group at carbon-16 (cf. I).

More recently Wenkert and Bringi[10] have drawn attention to the following limitations of the Barger-Hahn scheme: (a) it does not readily account for the predominantly aliphatic character of those indole alkaloids containing a carbocyclic ring E; (b) it is inconsistent with the observation that carbon-15 appears to possess a unique absolute configuration[10] (the single known exception being ψ-akuammicine[11]); (c) the postulated origin of the carbomethoxy group involving a tropolone intermediate is considered to be inadequate.

An ingenious alternative scheme was proposed by these authors in which the alicyclic precursors of phenylalanine, namely shikimic acid and prephenic acid were utilized directly. A key step in this subsequent hypothesis is a 1,2 migration of the pyruvyl side chain of a hydrated

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[7] E. Leete, Chem. & Ind. 692 (1960).

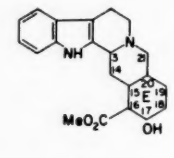
[8] A.J. Birch, D.W. Cameron, P.W. Holloway, R.W. Rickards, Tetrahedron Letters No.25, 26 (1960); K. Chambers, G.W. Kenner, M.J. Temple Robinson and B.R. Webster, Proc.Chem.Soc. 291 (1960).

[9] Sir Robert Robinson, Structural Relations of Natural Products p.110. Clarendon Press, Oxford (1955).

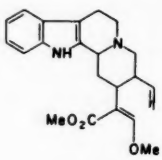
[10] E. Wenkert and N.V. Bringi, J.Amer.Chem.Soc. 81, 1474 (1959).

[11] P.N. Edwards and G.F. Smith, Proc.Chem.Soc. 215 (1960).

prephenic acid with the retention of configuration; in this respect the mode of formation of the substituted ring E carbon skeleton is less direct than that of the Barger-Hahn scheme, although a reasonable analogy was cited in the known pathway leading to homogentisic acid. The opening of ring E corresponding to the Woodward fission, is suggested by Wenkert and Bringi to involve the retro-aldol cleavage of a β-oxycyclohexanone ring.



I



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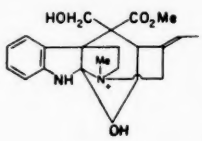

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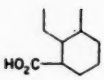

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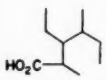

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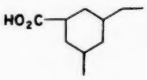
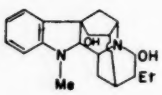
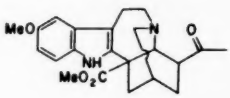


X

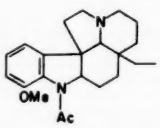
XI



V



VIII



IX

The primary value of such speculations to date, has been the biosynthetic correlation of two major types of C_{10} unit (VI and VII) among the indole alkaloids (existing also as C_9 units where the carbomethoxy group is absent). Two other variants of these C_{10} and C_9 units can be recognized in the indole alkaloids related to voacryptin (VIII)[12] and aspidospermine (IX),[13] the corresponding non-tryptamine moieties being derivatives of X and XI respectively.

[12] V. Renner and D.A. Prins, Experientia 17, 106 (1961).

[13] J.F.D. Mills and S.C. Nyburg, Tetrahedron Letters No.11, 1 (1959). H. Conroy, P.R. Brook and Y. Amiel, Ibid. No.11, 4 (1959).

The purpose of the present paper is to propose a relatively simple scheme for the biosynthesis of the indole alkaloids which appears to satisfy the above criteria. This can be best illustrated in terms of the C_{10}-pyridine alkaloid gentianine (XII), which also has the carbon skeleton VII and whose biosynthesis has been previously interpreted on the basis of both the Barger-Hahn-Woodward[14] and the Wenkert-Bringi[10] hypotheses. It is now suggested that a more direct route is one which would involve the ring fission of a cyclopentanoid monoterpene related to the alkaloids actinidine (XIII) and skytanthine (XIV).[15]

This alternative pathway could equally account for the origin of the glucosides oleuropein (possible structure XV,[16] which in some respects resembles emetine IV), swertiamarine (XVI),[17] and its related lactam bakankosin (XVII),[12] which all contain the C_{10} skeleton VII. Thus on structural grounds, their derivation from non-nitrogenous cyclopentanoid monoterpenes related to verbenalin (XX),[18] genepin (XVIII),[19] and asperuloside (XIX)[20] would be readily explicable.

It would appear to be particularly significant that the esterified carboxyl in most of these compounds is substituted at the carbon atom which would correspond to carbon-16 in yohimbine and the related 17,18-seco series. The absence of this carbomethoxy group in certain indole alkaloids

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[14] T.R. Govindachari, K. Nagarajan and S. Rajappa, Experientia 14, 5 (1958).

[15] C. Djerassi, J.P. Kutney, M. Shamma, J.N. Schoolery and L.F. Johnson, Chem. & Ind. 210 (1961); G.C. Casinovi, J.A. Garbarino and G.B. Marini-Bettolo, Ibid. 253 (1961).

[16] L. Panizzi, M.L. Scarpati and G. Oriente, Gazz.Chim.Ital. 90, 1449 (1960). For alternative structure, cf. B. Shasha and J. Leibowitz, J.Org.Chem. 26, 1948 (1961).

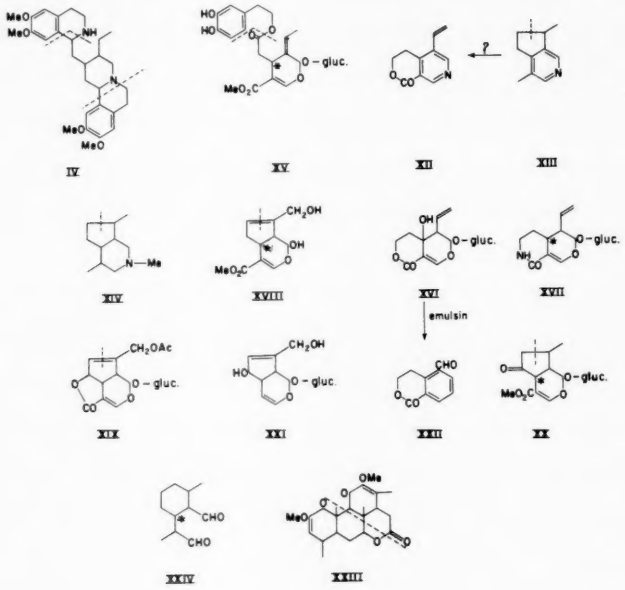
[17] T. Kubota and Y. Tomita, Tetrahedron Letters No.5, 176 (1961).

[18] G. Buchi and R.E. Manning, Tetrahedron Letters No.26, 5 (1960).

[19] C. Djerassi, T. Nakano, A.N. James, L.H. Zalkow, E.J. Eisenbraun and J.N. Schoolery, J.Org.Chem. 26, 1192 (1961).

[20] J. Grimshaw, Chem. & Ind. 403 (1961).

such as ajmaline and also in emetine, finds a parallel in the monoterpenoid series in the bitter substance aucubin (XXI).[21]



On the basis of these structural comparisons, e.g. between swertiamarin (XVI) and asperuloside (XIX), it would seem that unless a biosynthetic interrelationship is involved, the degree of coincidence would be remarkable. The above scheme could be reasonably extended to include the relevant indole alkaloids, with the proviso that the yohimbine alkaloids containing a homocyclic ring E (corresponding to VI) would result from the cyclization of a derivative of the acyclic C_{10} unit VII. This sequence is in direct contrast to that proposed in the previously mentioned hypotheses, however, an analogous ring closure is apparent in the enzymatic degradation of swertiamarin (XVI). Thus, following hydrolysis of the β-glucoside with emulsin, the aglucone

[21] S. Fujise, H. Obara and H. Uda, Chem. & Ind. 289 (1960); J. Grimshaw and H.R. Juneja, Ibid. 657 (1960).

undergoes cyclization to the benzenoid product erythrocentaurin (XXII)[17] (cf. the indole alkaloid alstoniline in which ring E is benzenoid).

A related homocyclic (non-aromatic) structure is contained in the bitter principle quassin whose probable structure (XXIII),[22] would on this basis require the oxidative coupling of two identical monoterpenoid units (containing the same carbon skeleton as VI), in a manner similar to the suggested mode of formation of gossypol.[23]

By analogy with swertiamarin, a parallel cyclization of oleuropein (XV) and also bakankosin (XVII) would yield a hydroaromatic ring in which the stereo-chemical integrity of the carbon asterisked in XV and XVII, would probably be maintained. This asymmetric centre would correspond to the hypothetical precursor of carbon-15 of ring E of the indole alkaloids. While the absolute configurations at this position in oleuropein and bakankosin have not yet been described, the equivalent carbon in genepin (XVIII) is known to be substituted by an α-hydrogen,[19] which is consequently in accordance with Wenkert and Bringi's criterion.[10] The same α-configuration has also been established for all the other members of this group of monoterpenoid compounds studied thus far, including verbenalin (XX), nepetalactone, the ant lactones iridomyrmecin and iridodial (XXIV) and the related product plumieride.[18,19,24]

A biosynthesis of iridodial has been proposed which involves the cyclization of citronellal and this mechanism was simulated in a laboratory synthesis.[25] The subsequently required cleavage of the cyclopentane ring

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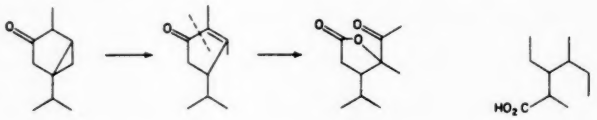
22 Z. Valenta, S. Papadopoulos and C. Podesva, Tetrahedron In press (1961); R.M. Catman and A.D. Ward, Tetrahedron Letters, No. 10, 317 (1961).

23 D.H.R. Barton and T. Cohen, Festschrift Arthur Stoll (Edited by A. Stoll) p.117. Birkhauser, Basle (1957).

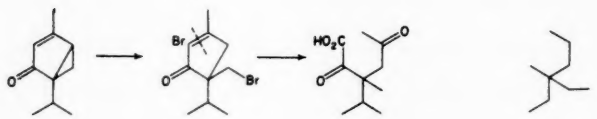
24 G.W.K. Cavill, Rev.Pure Appl.Chem. 10, 69 (1960).

25 K.J. Clark, G.I. Fray, R.H. Jaeger and Sir Robert Robinson, Tetrahedron 6, 217 (1959).

(leading to VII) finds an analogy in an established sequence of degradations of thujone (XXV).[26] Thus, under the influence of cold concentrated sulphuric acid, the cyclopropane ring of thujone is opened, yielding isothujone (XXVI) which possesses the same carbon skeleton as iridodial, genepin, etc. (this reaction is consequently compatible with an alternative biosynthetic derivation of the cyclopentanoid monoterpenes via the more commonly occurring cyclohexanoid series such as limonene). Isothujone can then undergo oxidative fission of the cyclopentane ring to give the keto lactone (XXVII), which contains the same carbon skeleton VII present in gentianine, oleuropein, swertiamarin and bakankosin, thus simulating the key step of the presently proposed biosynthetic scheme.



XXV XXVI XXVII VII



XXVIII XXIX XXX XI

The thujone analogue umbellulone (XXVIII) is known to undergo an alternative cleavage of the cyclopropane ring which may be significant in relation to the aspidospermine (IX) alkaloids. Thus, the bromination product dibromoumbellulone (XXIX) is a substituted cyclopentenone containing a quaternary carbon, which can be reduced with zinc and acetic acid to bromodihydroumbellulone and subsequently oxidized with permanganate to yield the diketo acid XXX.[26] An analogous biosynthetic sequence involving the loss of one

[26] P. de Mayo, Chemistry of Natural Products (Edited by K.W. Bentley) Vol. II, Chap. 3. Interscience, New York (1959).

of the gem-dimethyl groups through oxidation and decarboxylation (as is apparent in aucubin formation) would yield the carbon skeleton of the non-tryptamine moiety (XI) of aspidospermine and related alkaloids. These bases could therefore in theory be related to the yohimbine group through a common bicyclic monoterpene precursor of the thujone type. However, in view of the recognized facility with which the terpenes undergo rearrangement, this latter pathway represents only one of a number of possibilities.

It is similarly possible to arrive at various hypothetical schemes for the formation of the cyclohexanoid moiety of indole alkaloids related to voacryptin (VIII). However, it would be of primary importance to test the scheme in relation to the origin of the more common yohimbine group using labelled acetate and mevalonate (XXXI). If its validity could be verified in this way, then subsequent studies, as employed in the investigation of the biosynthesis of gibberellic acid[27] and trichothecin,[28] would provide information on the nature of the rearrangements involved in the construction of the units X and XI, present in voacryptin and aspidospermine respectively. The poor incorporation of acetate into trichothecin indicates the limited value of this precursor, relative to mevalonate, for the detection of terpenes.

Although the present concept, requiring the combination of tryptamine with a monoterpene is far removed from the Barger-Hahn and Wenkert-Bringi hypotheses, it would be entirely consistent with the recently elucidated mode of biosynthesis of another class of indole alkaloids, namely, the ergot group,[29] where the precursors were, in fact, shown to be tryptophan

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[27] A.J. Birch, R.W. Rickards, H. Smith, J. Winter and W.B. Turner, Chem. & Ind. 401 (1960).

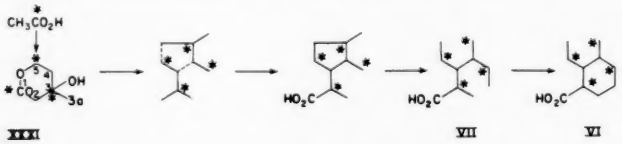
[28] J. Fishman, E.R.H. Jones, G. Lowe, and M.C. Whiting, Proc.Chem.Soc. 127 (1959).

[29] A.J. Birch, B.J. McLouglin and H. Smith, Tetrahedron Letters No.7, 1 (1960).

and mevalonic acid. Echinulin[30] is an isoprenoid fungal indole which is also probably derived from these precursors.

In summary, it is suggested on the basis of the structural relationships noted above, that the biosynthesis of gentianine, oleuropein, swertiamarin and bakankosin is related to that of the non-tryptamine moiety of the indole alkaloids and that the hypothetical pathway possesses the following features: (a) the C_{10} unit VII may be derived from two units of mevalonate via a cyclopentanoid monoterpene in such a way that the berberine bridge of yohimbine (carbon-21) would correspond to carbon-5 of this precursor (also equivalent to the carboxyl-carbon of acetate). The carbomethoxy group would be derived from either carbon 2 or 3a of mevalonate (equivalent to the methyl carbon of acetate). Neither ring E substituent would be specifically derived from C_1 units, as required by the earlier hypotheses; (b) the alkaloids containing the acyclic C_{10} unit VII would represent the skeletal precursors of the homocyclic ring E group (corresponding unit VI), which would be formed in an analogous manner to that involved in the cyclization of swertiamarin (XVI) to erythrocentaurin (XXII); (c) the C_{10} series (containing the units VI and VII) would be expected to represent the parent structures, giving rise to the C_9 series by decarboxylation.

The overall biosynthetic sequence may be outlined thus:



XXXI VII VI

In the specific instance of strychnine, in which the decarboxylated skeleton VII carries an additional C_2 unit, as pointed out by Woodward[3], this is probably derived from another acetate unit. The present scheme

[30] C. Cardini, G. Casnati, F. Piozzi and A. Quilico, Tetrahedron Letters No.16, 1 (1959).

would consequently require this part of the strychnine molecule to have a mixed acetate and mevalonate origin. This combination of precursors has been demonstrated by tracer studies to lead to mould products of widely differing structure, e.g. mycophenolic acid,[31] trichothecin[28] and herqueinone.[32] It is worth noting, however, that the carboxymethyl group on the side chain of mycophenolic acid, arises by the oxidative removal of the isopropyl component of an isoprenoid unit, thus providing a possible alternative to the direct incorporation of acetate into the lactam ring of strychnine, *via* the degradation of a cyclopentanoid sesquiterpene.

The present scheme is consistent with taxonomic considerations; thus, aucubin (XXI) from *Buddlea* spp. and bakankosin (XVII), which with a number of indole alkaloids occurs in the genus *Strychnos*, are examples of hypothetically related products from genera classified in the same family (*Loganaceae*). However, in view of the isolation of cyclopentanoid monoterpenes from ants, the significance of this association may be gratuitous. The principal advantage, relative to the two previously suggested hypotheses, is the considerable simplification of the steps required to arrive at the indole alkaloid non-tryptamine skeleton, *via* the rearrangement of a cyclic monoterpenoid precursor.

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[31] A.J. Birch, R.J. English, R.A. Massy-Westropp and H. Smith, *J.Chem.Soc.* 369 (1958).

[32] R. Thomas, *Biochem. J.* **78**, 807 (1961).

Tetrahedron Letters No. 16, pp. 554-559, 1961. Pergamon Press Ltd. Printed in Great Britain.

OXIDATION OF 3-KETO STEROIDS IN ALKALINE MEDIUM

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Laboratorio Ricerche chimiche, via dei Gracchi 35, Milano

(Received 24 July 1961)

WE have described in preceding publications [1,2] the preparation of 4-hydroxy-3-keto-Δ^4-steroids from the corresponding 3-keto-4,5-epoxides.

In this paper we report a new method for the synthesis of this class of compounds, consisting in the oxidation of 3-keto-5β-steroids in alkaline solution in the presence of air.

Transformations of ketones by the action of potassium alcoholate and oxygen have already been published: Doering[3] and Elkik[4] by oxidation in alkaline solution of ketones having α hydrogen obtained acids formed by breaking of C-C bonds. Barton obtained a diosphenol from a ketone present in the citrus bitter principle limonin[5] and introduced a 17α-hydroxy group in 20-keto saturated steroids.[6]

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[1] B. Camerino, B. Patelli and A. Vercellone, J.Amer.Chem.Soc. 78, 3540 (1956).

[2] B. Camerino, B. Patelli, A. Vercellone and F. Meda, Il Farmaco (Ed.Sc.) 11, 586 (1956); B. Camerino, R. Modelli and B. Patelli, Ibid. 13, 52 (1958).

[3] W. Doering and R.M. Haines, J.Amer.Chem.Soc. 76, 482 (1954).

[4] E. Elkik, Bull.Soc.Chim.Fr. 933 (1959).

[5] D.H.R. Barton, S.K. Pradham, S. Sternhell and J.F. Templeton, J.Chem.Soc. 255 (1961); see also Experientia 16, 41 (1960).

[6] D.H.R. Barton, E.J. Bailey and J. Elks, Proc.Chem.Soc. 214 (1960).

5β-Androstan-17β-ol-3-one[7] was dissolved in t-butanol containing potassium t-butylate and left at room temperature for 40 hours. After usual work-up we isolated 4-hydroxy-testosterone,[1] m.p. 221-223°, $[\alpha]_D^{22}$ + 102° ($CHCl_3$), ϵ_{278}^{EtOH} 11,900 in 50% yield. Since the isolation of pure 3-keto-5β-steroids is not always easy, we have in other instances used the crude products obtained by catalytic reduction of the corresponding 3-keto-Δ^4-steroids.

The reaction was followed by observing the increase of the U.V. absorption maximum at 278 mμ and required usually 18-50 hours. The yields were in the range of 20-60% of pure 4-hydroxy-Δ^4-3-keto-steroids, isolated by direct crystallization. All the compounds showed the expected enolic properties (ultra-violet, infra-red, ferric chloride) and were identified by comparison with authentic samples prepared as already described.[1,2] The steroids which were subjected to the reaction and the physical properties of the products isolated are reported in Table 1.

We have also applied this reaction to 3-keto-5α-steroids and we have isolated the corresponding 2-keto derivatives in enolic form. The structure of these compounds, which was different from the corresponding 4-hydroxy-3-keto-Δ^4-steroids, was deduced from the following facts:
(1) elementary analysis, (2) maximum at 267-270 mμ in the U.V., (3) red colour developed with $FeCl_3$, (4) H_2O_2 - NaOH oxidation of 17α-methyl-5α-androstane-17β-ol-2,3-dione to 2,3-seco-17α-methyl-5α-androstane-17β-ol-2,3-dioic acid identical with the acid obtained by oxidation of 17α-methyl-5α-androstane-17β-ol-3-one with CrO_3 - AcOH.[8]

In Table 2 are shown the products subjected to the reaction and the physical properties of the compounds obtained.

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[7] V. Prelog, L. Ruzicka, P. Meister and P. Wieland, Helv.Chim.Acta 28, 618 (1945).

[8] L.F. Fieser and M. Fieser, Steroids p.64. Reinhold, New York (1959).

TABLE 1 [a,b]

Properties of 4-Hydroxy-3-keto-Δ^4-derivatives

Starting material[c]	4-Hydroxy-3-keto-Δ^4-derivatives		
	m.p.	$[\alpha]_D^{22}$ in $CHCl_3$	ϵ_{278}^{EtOH}
17α-Methyltestosterone	173-175°	+ 70°	12,950
11β-Hydroxy-17α-methyltestosterone[9]	183-185°	+111°	12,380
19-Nortestosterone[10]	188-190°	+ 50°	11,600
17α-Methyl-19-nortestosterone[11]	168-170°	+ 26°	12,820
Progesterone	233-235°	+191°	12,200
17α-Hydroxyprogesterone	229-231°	+185°	11,850
Δ^4-Pregnen-3-one-BMD[d] [12]	280-285°	- 25°	12,900
Cortisone-BMD[13]	275-277°	+152°	10,200
Hydrocortisone-BMD[13]	268-270°	+ 13°	9,900

[a] Satisfactory analytical and spectral properties have been obtained for the new substances reported herein.

[b] All the 4-hydroxy-3-keto-Δ^4-steroids give with $FeCl_3$ in aqueous ethanol a dark green colour.

[c] Crude 4,5 dihydroderivatives obtained by Pd/C reduction of the following 3-keto-Δ^4-steroids.

[d] The designation BMD signifies bismethylenedioxy.

9 M.E. Herr, U.S.Pat. 2.793.218; Chem.Abstr. 52, 1298d (1958).

10 A.L. Wilds and N.A. Nelson, J.Amer.Chem.Soc. 75, 5366 (1953).

11 C. Djerassi, L. Miramontes, G. Rosenkraz and F. Sondheimer, J.Amer.Chem.Soc. 76, 4092 (1954).

12 R. Beyler and L.H. Sarett, U.S.Pat. 2.888.457.

13 R.E. Beyler, R.M. Moriarty, F. Hoffman and L.H. Sarett, J.Amer.Chem.Soc. 80, 1517 (1958).

TABLE 2

Properties of 2,3-Diketo-5α-derivatives [a]

Starting material	2,3-diketo-5α-derivatives			
	m.p.	$[\alpha]_D^{22}$ in $CHCl_3$	λ_{max}	ϵ
17α-Methyl-5α-androstane-17β-ol-3-one[14]	183-186°	+28°	270	7900
19-Nor-5α-androstane-17β-ol-3-one[15]	158-162°	+37°	237	8700[b]
5α-Pregnane-11β-ol-3-one-BMD[c]	260-262°	-38°	267	9340

[a] See Table 1, note a.

[b] The product of the reaction has been purified as the diacetate.

[c] Prepared from 5α-pregnane-11β,17α,21-triol-3,20-dione-21-acetate[16] by saponification and treatment with hydrochloric acid and formalin; the product had m.p. 235-240°.

It was also interesting to see if 3-keto-Δ^4-steroids reacted when submitted to the action of potassium t-butylate in the presence of air. When a solution of Δ^4-cholestene-3-one in t-butanol was subjected to the action of potassium t-butylate for 36 hours at 25° in an open flask, the absorption maximum at 240 mμ disappeared and two new maxima appeared at 255 and at 315 mμ. After the usual work-up and chromatography, we were able to isolate (15% yield) $\Delta^{4,6}$-cholestadiene-4-ol-3-one (diosterol 1),[17] m.p. 160-163°;

[14] L. Ruzicka, M.W. Goldberg and H.R. Rosenberg, Helv.Chim.Acta 18, 1487 (1953).

[15] A. Bowers, H.J. Ringold and E. Denot, J.Amer.Chem.Soc. 80, 6115 (1958).

[16] J. Pataki, G. Rosenkranz and C. Djerassi, J.Biol.Chem. 195, 751 (1952).

[17] H.H. Inhoffen, Ber.Dtsch.Chem.Ges. 69, 1702 (1936); A. Butenandt and G. Schramm, Ibid. 69, 2289 (1936).

TABLE 3

Properties of 4-Hydroxy-Δ^{6}-3-Keto-$\Delta^{4,6}$- and 3,6-Diketo-Δ^{4}-Derivatives[a]

Starting material	4-Hydroxy-Δ^{6}-dehydro-derivatives			6-Keto-derivatives		
	m.p.	$[\alpha]_D^{22}$	ϵ_{318}^{EtOH}	m.p.	$[\alpha]_D^{22}$	ϵ_{250}^{EtOH}
Testesterone	210-215°	+ 80°[b]	21,200	205-210°	-49°[c]	10,600[19]
17α-Hydroxyprogesterone-20-ethylenketal[20] [e]	263-265°	+102°[d]	23,760	250-252°	-60°[b]	10,300[22]
Cortisone-EMD[13]	310-315°	+145°[b]	20,300	248-250°	-11°[d]	10,460
Hydrocortisone-EMD[13]	288-290°	+ 23°[d]	20,670	288-290°	-79°[b]	10,760
9α-Fluorohydrocortisone-EMD[12]	300-305°	+ 44°[d]	21,480	-	-	-

[a] See Table 1, note a.

[b] In chloroform solution.

[c] In acetone solution.

[d] In dioxane solution.

[e] The data reported for the 4-hydroxy-Δ^{6}-dehydro- and 6-keto-derivatives refer to the products obtained after acid hydrolysis of the ketal group.

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ϵ_{315}^{EtOH} 21.400; $[\alpha]_D^{22}$ +36° ($CHCl_3$) and (5% yield) Δ^4-cholestene-3,6-dione;[18] m.p. 123-125°; ϵ_{251}^{EtOH} 10.500; $[\alpha]_D^{22}$ -37°.

The same reaction was applied to the following steroids (see Table 3).

It is possible to reduce selectively the Δ^6 double bond of 4-hydroxy-$\Delta^{4,6}$-3-keto-steroids; in fact 4-hydroxy-Δ^6-testosterone yields by hydrogenation with Pd/C 4-hydroxy-testosterone.[1]

The 3,6-diketo-Δ^4-steroids possess characteristic I.R. absorption spectra which will be the subject of a future communication by one of us (R.S.).

The oxidations described probably proceed through the attack of oxygen on the anion formed by enolization of the ketone in alkaline medium. It is well known[21] that 3-keto-5β-steroids enolize to 3-hydroxy-Δ^3-compounds while the 5α epimers give 3-hydroxy-Δ^2-steroids; the attack of oxygen takes place on the former at C_4 and on the latter at C_2. In the case of 3-keto-Δ^4-steroids which by enolization give a 3-hydroxy-$\Delta^{3,5}$-diene, the attack of oxygen takes place in position 4 or 6.

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18 J. Mauthner and W. Suida, Monatsh. 17, 579 (1896); W.C.J. Ross, J.Chem.Soc. 737 (1946).

19 A. Butenandt and B. Riegel, Ber.Dtsch.Chem.Ges. 69, 1163 (1936).

20 P.L. Julian, E.W. Meyer and I. Ryden, U.S.Pat. 2.648.662; Chem.Abstr. 48, 7651 (1954).

21 See ref. 8, p.282.

22 P.D. Meister, D.H. Peterson, H.C. Murray, G.B. Spero, S.H. Eppstein, A. Weintraub, L.M. Reineke and H.M. Leigh, J.Amer.Chem.Soc. 75, 416 (1953); Makoto Shirasaka, Chem.Pharm.Bull.(Japan) 9, 152 (1961).

Tetrahedron Letters No. 16, pp. 560-564, 1961. Pergamon Press Ltd. Printed in Great Britain.

ULTRAVIOLET SPECTRAL MEASUREMENTS ON ISOLATED DOUBLE BOND SYSTEMS

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(Received 22 August 1961)

RECENTLY, Reichstein and co-workers[1] and Ellington and Meakins[2] reported the ultraviolet absorption spectra of isolated double bonds (particularly in steroids and triterpenoids) measured with nitrogen-flushed, conventional spectrophotometers. The results lacked variation with structure below 195 mμ and appeared in considerable disagreement with Turner's study using a vacuum spectrophotometer.[3] These factors and an interest in the spectra of polycyclic compounds led us to a re-examination of the 175-205 mμ region. This preliminary communication was prompted by recent reports of studies relying on conventional spectrophotometers: (1) an attempt by Chapman and Parker[4] to resolve the above differences, (2) the apparent acceptance by Swiss researchers[5,6] of methods credited to Reichstein and co-workers,[1] and (3) the current interest in interaction studies utilizing measurements in this spectral region.[7] The limitations and some sources of error with such

[1] K. Stich, G. Rotzler and T. Reichstein, Helv.Chim.Acta 42, 1480 (1959).

[2] P.S. Ellington and G.D. Meakins, J.Chem.Soc. 697 (1960).

[3] D.W. Turner, J.Chem.Soc. 30 (1959).

[4] J.H. Chapman and A.C. Parker, J.Chem.Soc. 2075 (1961).

[5] C.H. Grob and A. Weiss, Helv.Chim.Acta 43, 1390 (1960).

[6] H.P. Sigg and Ch. Tamm, Helv.Chim.Acta 43, 1402 (1960).

[7] S. Winstein, L. De Vries and R. Orloski, J.Amer.Chem.Soc. 83, 2020 (1961).

instruments were recognized but many of the reports[1,2,4] seemed overly optimistic as to the lower limits of reliability. Consequently, structure-spectral relationships based on such results could lead to erroneous conclusions regarding interaction or positional effects. The following discussion stresses some of these discrepancies, suggests probable sources of error, and notes methods of assessing the limitations of the measuring systems.

Our measurements were made using a Beckman "Extended-UV-Range" DK-2 spectrophotometer[8] designed for operation down to 170 mμ.[9] This instrument has excellent stray light characteristics: < 0.5% at 180 mμ with a Corning #7905 Vycor filter with 1% T at 220 mμ; < 2% at 180 mμ with doubly-distilled water (in a special, high transmissivity, 0.1 cm cell provided by the manufacture), if the 2.25 absorbance of the water determined from measurements in a 0.01 cm cell is taken into account. If stray light at 180 mμ is 2%, the maximum error in observed absorbances < 0.5 will not exceed 4%[10] and, since the stray light becomes essentially zero at 185 mμ, this error becomes insignificant. By use of cyclohexane (purified through Davison #923 silica gel) in one-piece stoppered quartz cells (sample 0.011 cm, reference 0.010 cm),[11] errors due to solvent absorbance[12] can be corrected for or are negligible since this cyclohexane has 80% transmittance in 0.01 cm cells at 180 mμ.

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[8] Reference to a company or product name does not imply approval or recommendation of the product by the Department of Agriculture to the exclusion of others that may be suitable.

[9] "Spectroscopy in the Region 175-200 mμ" by Wilbur Kaye, Beckman Instruments, Inc., Reprint R-6150, adequately discusses the special instrumentation and precautions for operation in this region.

[10] K.S. Gibson in M.G. Mellon, Analytical Absorption Spectroscopy pp. 247-248. John Wiley, New York (1950).

[11a] American Instrument Co., Silver Springs, Md.; [b] We are indebted to Mr. G.F. Bailey for these measurements.

[12] D.D. Tunnicliff, Talanta 2, 341 (1959), has discussed the types of errors influenced by solvent absorbance.

The validity of our measuring system was established by comparison with published data obtained with vacuum instruments. The ϵ values from the spectrum of cyclohexene are offered as an example (Fig. 1), and our λ_{max} 183.5 mμ, ϵ_{max} 7750 agree with those found using vacuum instruments, i.e. λ_{max} 183 mμ, ϵ_{max} 7500;[3] λ_{max} 183.5, ϵ_{max} 7400[13]; λ_{max} 183, ϵ_{max} 6800 $\pm$ 700.[14] That the maximum near the limit of our system cannot be due to stray light is substantiated by the minimum at 183 mμ in the curve for cholesteryl acetate (Fig. 1). As pointed out by Johnson[15], a minimum in the absorbance curve is much more convincing evidence of low stray light than a maximum.

Earlier values[1,2] for cholesteryl acetate (Fig. 1) are in excellent agreement with our values from 210 to 200 mμ, but at about 197 mμ they diverge and indicate spurious maxima at 193 mμ[1] or near 195 mμ.[2] Similarly, the data of Chapman and Parker[4] (λ_{max} 189 mμ, ϵ_{max} 8000), while indicating a maximum at 189 mμ, showed an ϵ value about 18% lower than ours (λ_{max} 187 mμ, ϵ_{max} 9700). Thus, it appears that these results,[1,2,4] while either corrected for[1] or low in[4] far stray light, suffered from errors due to near stray light coupled with insufficient energy at the wavelengths below 195-197 mμ. This latter effect could arise from solvent absorbance in the 0.1 cm cells used,[1,2,4] and from deterioration of instrument components. The errors due to the use of non-transparent solvents, such as ethanol, were discussed[4] in assessing other[2] results. However, unknown variation in path length, uncontrolled solvent loss via evaporation, and neglected errors due to stray light below 220 mμ detract from the significance of the data reported by Chapman and Parker[4].

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[13] H.B. Klevens and J.R. Platt in Chicago University, Dept. of Physics, Laboratory of Molecular Structure and Spectra Technical Report, 1953/54, part 1, p.145, Chicago (1954), ASTIA-AD 53029.

[14] W.J. Potts, J.Chem.Phys. 23, 65 (1955).

[15] E.A. Johnson, Unicam Spectrovision No. 8, 1 (1960).

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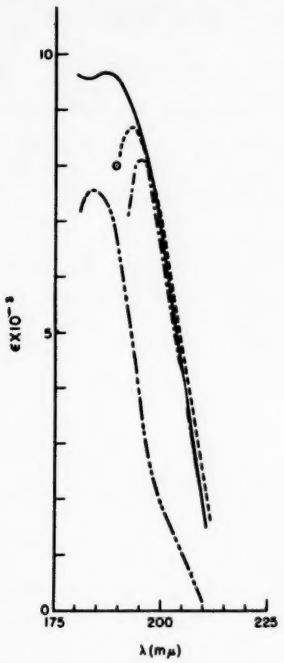

Fig. 1. Absorption spectra of cholesteryl acetate: from data of Stich, Rotzler and Reichstein[1], _ _ _ _ ; from data of Ellington and Meakin[2], ___ _ ___ _ ; and from datum of Chapman and Parker[4]. Also shown are the results observed for cholesteryl acetate, _____ ; and cyclohexene, ___ _ _ ___ _ _ .*

Apparently, satisfactory λ_{max} and ϵ_{max} values are not obtainable much below 193-195 mμ with conventional spectrophotometers.[16] We would strongly urge that such ultraviolet instruments be carefully assessed with reference compounds, e.g. cyclohexene, cholesteryl acetate, and Δ^4-cholestene (λ_{max} 193 mμ, ϵ_{max} 10,000). This precaution would permit a resonable and reliable

* All compounds used were purified until they had physical properties comparable to those in standard reference works.

16 Measurements[11b] on a conventional instrument to 181 mμ with nitrogen-flushing produced divergence of spectral curves at 195-197 mμ much like that noted here.

lower limit to be established. Also of merit is the use of very short paths, e.g. 0.01 cm. The mere observation of low stray light originating above 220 mμ or the appearance of maxima do not necessarily constitute assurance of reliable measurements.

Other observations and correlations of spectra with structure (including ketones) made during this work will be published in a more detailed account of this study.

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Tetrahedron Letters No. 16, pp. 565-572, 1961. Pergamon Press Ltd. Printed in Great Britain.

PHOTOCHEMICAL TRANSFORMATIONS. IX.

TOTAL STRUCTURE OF SUPRASTEROL II[1,2]

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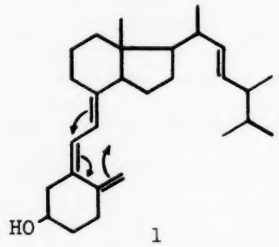
Department of Chemistry, University of California

Berkeley, California

(Received 31 July 1961; in Revised Form 5 September 1961)

In a previous communication,[3] it was shown that the structure of suprasterol II, a photochemical transformation product of Vitamin D_2 (1), was most likely represented by formula 2. We now wish to present evidence which establishes the correctness of structure 2 and its absolute stereochemistry as depicted by structure 25.



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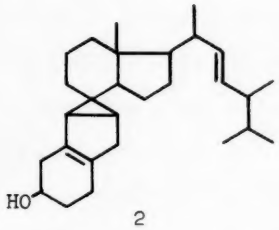

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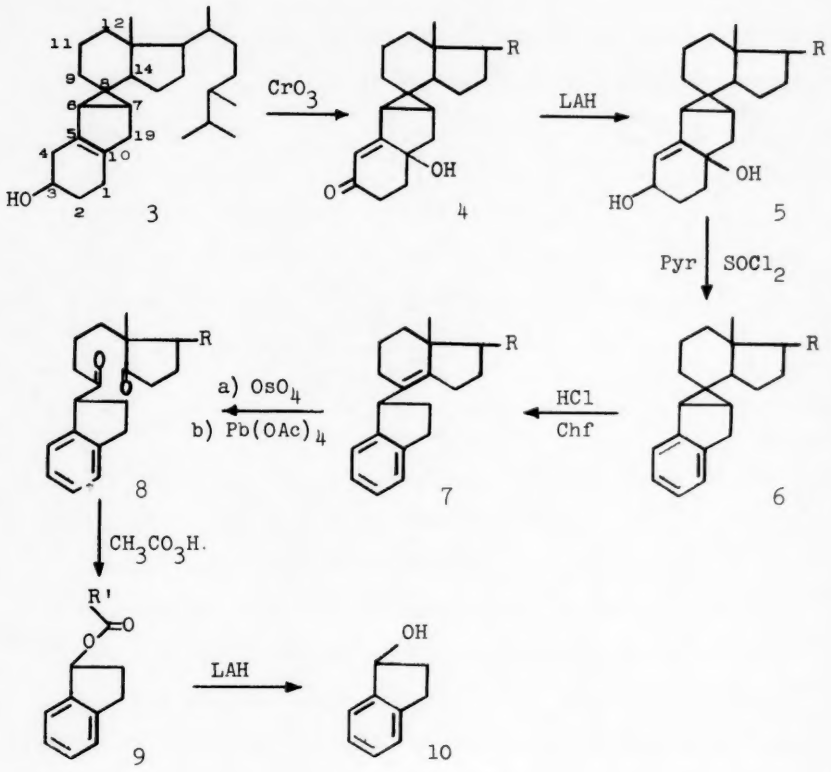
[1] For Paper VIII, see W. G. Dauben and R. L. Cargill, Tetrahedron, in press.

[2] This work was supported, in part, by Grant No. A-709 (C8), U. S. Public Health Service.

[3] W. G. Dauben, I. Bell, T. W. Hutton, G. F. Laws, A. Rheiner, Jr. and H. Urscheler, J. Am. Chem. Soc. 80, 4116 (1958).

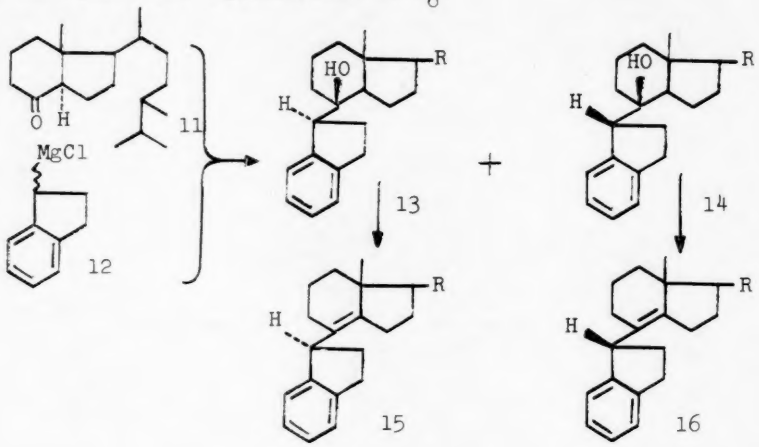
22-Dihydrosuprasterol II (3), upon oxidation with chromic acid in pyridine, was converted into hydroxyenone 4 (m.p. 227° $[\alpha]_D^{Chf}$ -80°, λ_{max}^{EtOH} 263 mμ (ε 13,100), ν_{max} 1670 cm $^{-1}$). The same product was obtained by epoxidation followed by oxidation under Oppenauer conditions. Lithium aluminum hydride reduction of 4 yielded the allylic diol 5 (m.p. 189°, λ_{max}^{EtOH} 211 mμ (ε 8,500)), which, upon dehydration at -15° with thionyl chloride in pyridine, gave the hydrocarbon 6 (oil, $\lambda_{max}^{cyclohexane}$ 280, 273, 259, 228, 202 mμ (ε 1,670, 1,760, 1,840, 9,000, 25,000)). The nmr spectrum of 6 showed the presence of four benzenoid protons and no vinyl protons. Upon treatment with hydrogen chloride in anhydrous chloroform, 6 rearranged to a mixture of isomeric unsaturated hydrocarbons (oil, $[\alpha]_D^{Chf}$ + 79°) in which 7 was present to an extent of greater than 80% (GLC analysis).[4] The U.V. spectrum ($\lambda_{max}^{cyclohexane}$ 273, 266, 259 mμ (ε 1,760, 1,930, 1,990) of the mixture was almost identical with that of indane, indicating that the double bond formed was not in conjugation with the benzene nucleus. The nmr spectrum of the mixture established the presence of less than 0.2 vinyl proton, showing the tetrasubstituted nature of the newly formed double bond. The mixture was osmylated and the diols were separated by alumina chromatography. The two

[4] W. J. A. Vanden Heuvel, C. C. Sweeley and E. C. Horning, J. Am. Chem. Soc. 82, 3481 (1960).



main products (oils, 40% and 22%, $\lambda_{max}^{cyclohexane}$ 273, 266, 260 mμ (ε 1,500, 1,400, 1,000)), upon oxidation with lead tetraacetate, gave the same oily diketone 8 ($\lambda_{max}^{cyclohexane}$ 273, 266, 260 mμ, ν_{max} 1740, 1710 cm $^{-1}$). The diketone 8 was allowed to react with peracetic acid and the ester-δ-lactone 9 was obtained (oil, ν_{max} 1740, 1710 cm $^{-1}$). Reduction of 9 with lithium aluminum hydride yielded a mixture from which 1-indanol 10 was isolated by alumina chromatography. The 1-indanol has $[\alpha]_D^{Chf}$ -10° as compared to $[\alpha]_D$ -34° for the

optically pure enantiomer,[5] indicating that the diketone 8 must have partially equilibrated at C_6.



To establish the structure of the acid catalyzed rearrangement product, hydrocarbon 7, 1-indanylmagnesium chloride 12 was allowed to react with the C_{19}-ketone 11, obtained from Vitamin D_2,[6] and the two alcohols 13 and 14, separated by alumina chromatography, were obtained in a ratio of 2.4:1. Dehydration of each alcohol yielded the related unsaturated hydrocarbon 15 ($[\alpha]_D^{Chf}$ -13°) and 16 ($[\alpha]_D^{Chf}$ + 63°), respectively. The hydrocarbon 16, derived from the minor alcohol 14, was identical with the hydrocarbon 7 obtained from degradation of suprasterol II and when degraded by the

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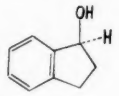
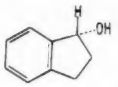
[5] W. Hückel and F. Mössner, Ann. 637, 57 (1960).

[6] H. H. Inhoffen, G. Quinkert, S. Schütz, G. Fredrich and E. Tober, Chem. Ber. 91, 781 (1958). A. Windaus and W. Grundmann, Ann. 524, 295 (1936).

same route as used above yielded the negatively rotating 1-indanol 10. These results establish the gross structure of suprasterol II as 2.[7]

Next, the stereochemistry of suprasterol II must be considered. In the formation of this irradiation product of Vitamin D_2 only the carbon atoms in the original triene





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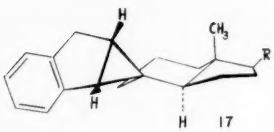

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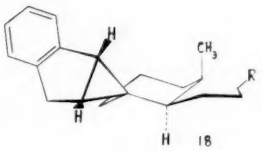

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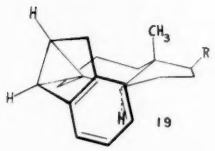

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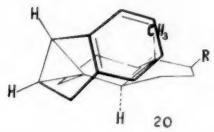

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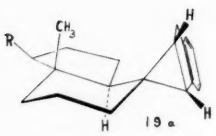

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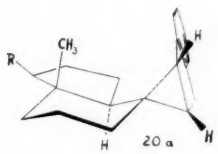

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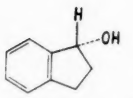

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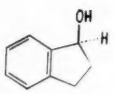

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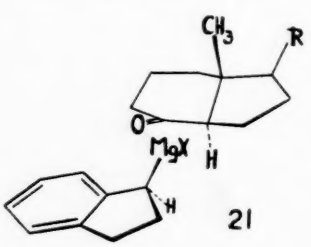
[7] Satisfactory analytical results have been obtained for all new substances reported. The purity of the oily materials was ascertained by paper chromatography (phenyl cellosolve-hexane) and by thin layer silicic acid chromatography.

system are involved, the other centers remaining as originally present in the steroidal starting material. The transformation of suprasterol II (2) to the aromatic hydrocarbon 6 does not affect the new centers C_6, C_7 and C_8, and determination of the configuration of these latter centers in 6 leads to a complete stereochemistry of 2. With the assumption that a three membered ring can only be fused to a five membered ring in a cis fashion, there are four possible steric arrangements for 6, i.e. 17, 18, 19 and 20. If the degradation of these four isomers to optically active 1-indanol by the above described route proceeds with retention of configuration, it is seen that 17 and 20 should yield one antipode of 1-indanol and 18 and 19 the other antipode. Thus, knowledge of the absolute configuration of 1-indanol would decrease the number of possible structures to two.

The absolute configuration of 1-indanol was determined by evaluation of the steric course of the reaction between the C_{19}-ketone 11 and the 1-indanylmagnesium chloride 12. The topside of ketone 11 is shielded by the angular methyl group and the approach of the bulky Grignard reagent 12 should be limited to the bottom-side as depicted below. The racemic Grignard



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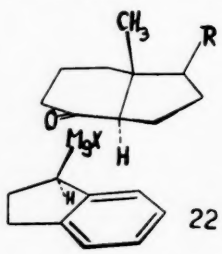
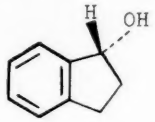


22

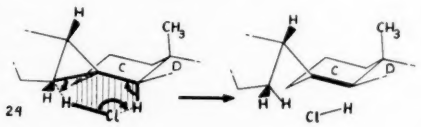
can add in two fashions, 21 and 22, to yield the two alcohols 13 and 14. Due to the lesser steric interactions of the two bulky reagents in pathway 21, the alcohol 13 should be the major product and the alcohol 14 the minor product. These latter two projections show the absolute configuration of the alcohols since the starting ketone is of known absolute stereochemistry. Recalling that the minor Grignard product 14 was the precursor of the hydrocarbon 6 which, upon degradation, yielded (-)-1-indanol, this antipode must have the absolute configuration 23.



23

1-Indanol of this configuration is derivable only from structures 18 and 19.

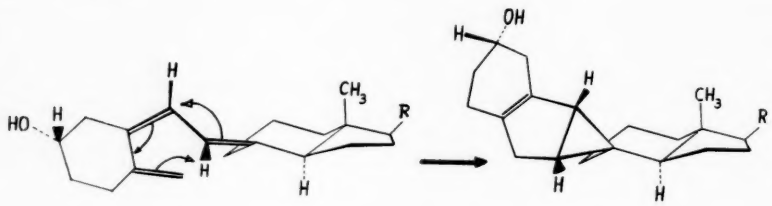
Consideration of the steric aspects of the cyclopropane ring opening permits differentiation between these two remaining structures. The formation of only olefins with isolated double bonds indicates that a carbonium ion type of intermediate involving C_6 does not intervene in the ring opening reaction since such an intermediate should yield some conjugated isomer. The selectivity of the conversion of 18 to 7 can be rationalized by



postulation of a cyclic six membered transition state (24) which does not involve C_6.

1961

Examination of 19a, a projection obtained by turning 19 by 90°, clearly shows that such a transition state is impossible for this isomer. On the basis of these mechanistic considerations, it is suggestive that the absolute stereochemistry of the hydrocarbon 6 is shown by 18. If such be the case, it follows that the total structure of suprasterol II is 25. Such a structural arrangement also suggests that the transformation of Vitamin D_2 (1) to suprasterol II (25) may proceed via the concerted process shown below.



25

Hodgkin and Sanderson (see following Letter), using X-ray diffraction, have determined the structure of suprasterol II and have established the correctness of structure 25.

Tetrahedron Letters No. 16, pp. 573-578, 1961. Pergamon Press Ltd. Printed in Great Britain.

THE CRYSTAL STRUCTURE OF SUPRASTEROL II

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Oxford, England

(Received 31 July 1961)

The molecular structure of suprasterol II has been investigated through the X-ray analysis of its 4-iodo-5 nitrobenzoate. This derivative was prepared and kindly supplied by Dr. J. W. Cornforth. Crystals for photography were obtained by recrystallization from hot benzene solution and occur as yellow plates with (100) the dominating face. They are monoclinic, with space-group C 2 and cell dimensions

$a = 39.14$ Å, $b = 10.34$ Å, $c = 8.21$ Å, and $\beta = 94° 51'$

The observed density is 1.32_5 gm.cm.$^{-3}$, corresponding with four molecules in the unit cell, for which the calculated density is 1.347 gm.cm.$^{-3}$.

The crystals were first examined in 1951 by M. Curzon[1] who measured the intensities of the hol and hko reflections, found the positions of the iodine atoms from Patterson projections based on these, and calculated trial electron density projections. These showed so much overlapping of

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[1] M. Curzon, Chemistry Part II, Thesis, Oxford University, (1951).

atomic positions that they could not be interpreted in any detail. Further work on the molecule was, therefore, deferred until a three-dimensional investigation could be more easily undertaken.

The present investigation began with the collection of three-dimensional data from equi-inclination Weissenberg photographs; the intensities of 1991 reflections were estimated visually and corrected for Lorentz and polarization factors; the reflections faded out at sin θ values of about 0.7. A three-dimensional Patterson synthesis was then computed from the derived F^2 values modified to correspond approximately with those from point atoms at rest, and from this synthesis the positions of the iodine atom, the benzene ring and the carboxyl group were determined. Structure factors were computed using these atomic positions, and were followed by the calculation of a three-dimensional Fourier synthesis based on the phase angles so derived. This electron-density map showed over eighty peaks of approximately one electron per $\mathring{A}^3$ in height, plus ten much higher peaks corresponding to those atoms included in the structure factor calculation. Most of the low peaks consisted of mirror-image pairs, the mirror planes occurring at $y = 0$ and $y = \frac{1}{2}$. This doubling was caused by the iodine positions being related by a mirror plane perpendicular to the y axis. It was possible to select one peak from each of 22 mirror-image pairs, using only the criteria of reasonable inter-atomic distances and angles. In most of these cases the

peak selected was slightly higher than its related peak.

A second set of structure factors was then computed using the positions of 32 atoms, and followed by a second Fourier synthesis. From this map five more atomic positions were determined in a similar manner, and a difference map based on a third set of structure factors showed the last four atoms. Least squares refinement is now proceeding and the R factor is at present 13.0%. It seems clear that the atoms have been placed well enough to define the outline molecular structure though not with high precision; at the present stage of the analysis carbon-carbon bond distances in the benzene ring vary between 1.29 and 1.60 Å, average 1.43 Å while single carbon-carbon bonds in the molecule as a whole vary from 1.26 to 1.73 Å, with an average of 1.53 Å.

The structure found, shown in Fig. 1 and Fig. 2,

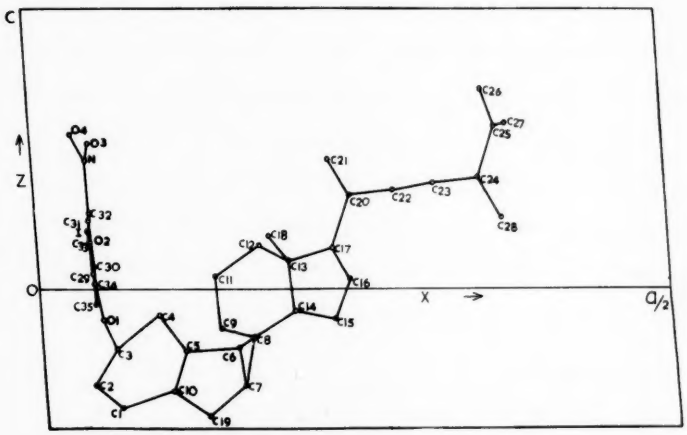

FIG. 1. Suprasterol II: projection of the molecule on (010).

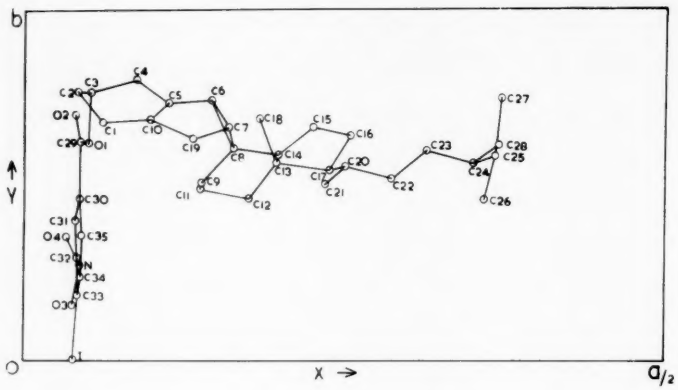

FIG. 2. Suprasterol II: projection of the molecule on (001).

agrees with that put forward by Dauben and Baumann[2] and formulated as I. In the suprasterol molecule a three-membered ring, fused to a five-membered ring, is attached through a spiro junction to ring C and replaces ring B of the original sterol skeleton. The five-membered ring is planar within the limits of experimental error, and carbon atoms 1 and 4 also lie in the plane of the ring as would be expected if C5 and C10 are joined by a double bond. Ring C and D of the sterol skeleton and the attached side chain appear in the same configuration as that found in calciferol, ring D being non-planar, with C17 deviating

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[2] Preceding letter, compare W. G. Dauben, I. Bell, T. W. Hutton, G. F. Laws, A. Rheiner, Jr. and H. Urscheler, J. Am. Chem. Soc. 80, 4116 (1958).

most from the plane of the remaining atoms. As a whole, the structure can be derived by comparatively small changes from that of calciferol itself[3] (II), where already C19 and C7 are so close that they impose a twisted form on the

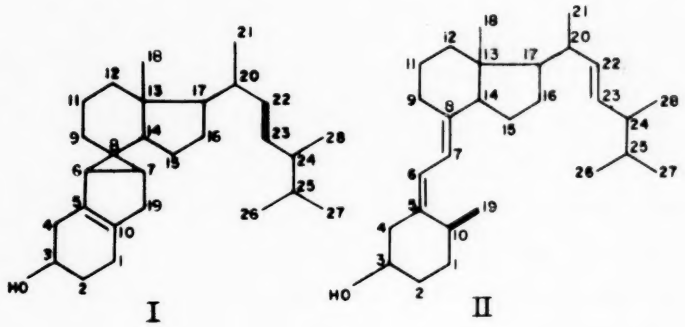

FIG. 3

cis butadiene group in the molecule. The movement of the double bond to link C5 and C10 flattens the molecule in this region of ring A in suprasterol, as described above, and this flattening is accompanied by a further conformational change. The hydroxyl group in this particular derivative of suprasterol II is in the erect, not equatorial, orientation and this carries the attached benzene ring into a position nearly perpendicular to the main planes of the

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[3] D. C. Hodgkin, M. S. Webster and J. D. Dunitz, Chem. and Ind. 1957, 1148.

steroid rings. This arrangement does not seem to be a necessary consequence of the changed stereochemical form of ring A and may result from packing conditions within the molecule and crystal structure. It has the effect of imposing a compact, rather than extended, shape on the molecule as a whole.

All computations were performed on the Oxford University MERCURY Computer. We wish to thank Dr. J. S. Rollett for his structure factor and least squares program, Dr. O. S. Mills for the use of his Fourier synthesis program, and the Oxford Computing Laboratory staff for their help and co-operation. One of us also wishes to thank the National Research Council of Canada for the award of a Special Scholarship.

Tetrahedron Letters No. 16, pp.579-582, 1961. Pergamon Press Ltd. Printed in Great Britain.

THE REACTION OF CARBETHOXYMETHYLENETRIPHENYLPHOSPHORANE WITH KETONES

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The Hungarian Academy of Science, Budapest

(Received 14 August 1961)

CARBALKOXYMETHYLENETRIPHENYLPHOSPHORANES of the general formula I ($R_1 = CH_3$, C_2H_5; $R = H$, CH_3) were used in the syntheses of a number of α,β-unsaturated esters and acids,[1] however, they were considered to be unable to undergo Wittig-reaction with ketones.[2] Our experiments do not bear out this view.

$$(C_6H_5)_3P{=}\underset{R}{C}\text{-}COOR_1 + O{=}C\begin{matrix}R_2\\R_3\end{matrix} \longrightarrow \begin{matrix}R_2\\R_3\end{matrix}C{=}C\text{-}COOR_1 + (C_6H_5)_3P{=}O$$

I

$R_1 = CH_3$, C_2H_5; $R = H$

$R_2 = CH_3$, C_6H_5

$R_3 = CH_3$, C_2H_5, C_6H_5

$R_2\text{-}R_3 = CH_2(CH_2)_nCH_2$

$n = 2, 3$

Carbethoxymethylene- or carbomethoxymethylenetriphenylphosphorane were found to react with ketones of rather different character when the components were heated in a sealed tube at 100° or, for a shorter time, at 170° (See Table 1).

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[1] O. Isler, H. Guttmann, M. Montavon, R. Ruegg, G. Ryser and P. Zeller, Helv.Chim.Acta 40, 1242 (1957); for further references see : U. Schöllkopf, Angew.Chem. 71, 260 (1959).

[2] S. Trippett and D.M. Walker, J.Chem.Soc. 1266 (1961).

TABLE 1

Reaction of Phosphorane I (R = H ; R_1 = C_2H_5) with Ketones

Ketone	Acid produced	Temp. (°C)	Time (hr)	Yield (%)	M.p. (°C)
Me_2CO	$Me_2C{:}CH.COOH$	100	24	44.5	69.5-70[a]
Me.CO.Et	Me(Et)C:CH.COOH	100	24	42	44-45[b]
		170	10	43	63-64[c]
		170	10	60	89.5-91.5[d]
Ph.CO.Me	Ph(Me)C:CH.COOH	170	10	58	76-78[e]
Ph_2CO	$Ph_2C{:}CH.COOH$	170	10	54	162-163[f]

[a] G.A.R. Kon and R.P. Linstead, J.Chem.Soc. 127, 624 (1925).
[b] G.A.R. Kon, R.P. Linstead and J.M. Wright, J.Chem.Soc. 599 (1934).
[c] O. Wallach, Leibigs Ann. 365, 273 (1909).
[d] H. Schmid and P. Karrer, Helv.Chim.Acta 31, 1067 (1948).
[e] R. Stoemer, F. Grimm and E. Laage, Ber.Dtsch.Chem.Ges. 50, 959 (1917).
[f] H. Rupe and E. Busolt, Ber.Dtsch.Chem.Ges. 40, 4537 (1907).

Experiments have been performed with different molar ratios of the reactants between the two extremes of 1:1 and 20:1 (ketone : phosphorane). The yields seemed to be practically unaffected by the excess of ketone present above the molar ratio 2:1 when the components were heated at 100° for 10 hours. (See Table 2.)

TABLE 2

Molar ratio of acetone to I (R=H;R_1=C_2H_5)	1	0.5	0.1	0.05
Yield %	38	43	40	44.5

No product of rearrangement to the more stable "enyl-acetic acid" was observed either with cyclohexanone or cyclopentanone even if reactions were accomplished at 170°. Products from the two "mixed" ketones, methylethylketone and acetophenone, consisted of cis and trans isomers as evidenced by melting point determinations. The trans-β-ethylcrotonic acid produced contained only a negligible quantity of the cis isomer which could be eliminated by several recrystallizations from alcohol-water mixture. Reaction of acetophenone with carbethoxymethylene triphenylphosphorane furnished, however, a comparable quantity of both isomers. This mixture afforded pure trans acid through acidic isomerization. A "one-pot" reaction between dialkyl carbalkoxyalkylphosphonate anions and alkyl halides has recently been reported[3] for the synthesis of acrylic ester derivatives. An analogous reaction between carbalkoxymethylene triphenylphosphorane and alkyl or aralkyl halides (CH_3J, $CH_2{:}CH.CH_2Br$, $C_6H_5CH_2Cl$) failed in our hands to take place.

Experimental

A typical procedure is as follows:

Carbethoxymethylenetriphenylphosphorane[1] (3.5 g) dissolved cyclohexanone (15 ml) by gently warming, was poured into a Pyrex glass tube (40 cm long and 1.8 cm diameter) which had been flushed with dry nitrogen. After filling the tube, it was flushed with nitrogen once more, and sealed over a blowpipe as rapidly as possible. After cooling to room temperature occasionally the separation of crystals could be observed. The tube was opened and its content transferred into a small distilling flask. Distillation was continued (at 15 mm) until no more cyclohexanone came over. The residue was treated with anhydrous petroleum ether (b.p.50-60°) and the crystals precipitated were filtered with suction, and recrystallized from benzene to give 2.6 g of pure triphenylphosphine oxide, m.p. 157-158°. The filtrate was concentrated

[3] W.S. Wadsworth and W.D. Emmons, J.Amer.Chem.Soc. 83, 1733 (1961).

and the residue saponified by boiling with alcoholic aqueous sodium hydroxide for several hours. The solution was diluted with water and most of the ethyl alcohol was evaporated under reduced pressure. The alkaline solution was extracted several times with ether to remove non-acidic components, then acidified to pH = 3 with hydrochloric acid, and extracted three times with 20 ml portions of ether. The combined ethereal solution was dried over anhydrous sodium sulphate. After evaporating the solvent under reduced pressure the residue was recrystallized from aqueous ethyl alcohol to give 0.85 g(60%) cyclohexylidene-acetic acid, m.p. 89.5-91.5° (reported[4] 92°). (Found: C, 68.41; H, 8.93. Calc. for $C_8H_{12}O_2$ (140.18): C, 68.52; H, 8.68%).

[4] E.H. Rodd (Editor), Chemistry of Carbon Compounds Vol. II, Part A, p.228. Elsevier, Amsterdam (1953).

Tetrahedron Letters No. 17, pp. 583-586, 1961. Pergamon Press Ltd. Printed in Great Britain.

1.3 DIPOLARE ADDITIONEN DER NITRILOXYDE AN CARBONYLVERBINDUNGEN

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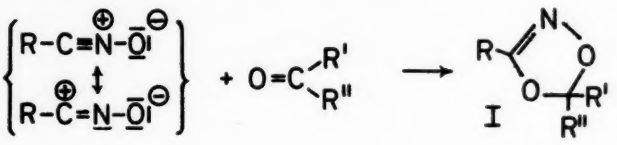
Institut für Organische Chemie der Universität München

(Received 12 September 1961)

NITRILOXYDE vermögen sich mit der Carbonylgruppe von Aldehyden, α-Ketoestern und α-Diketonen in 1.3-Dipolarer Addition [1] zu 1.3.4-Dioxazolen zu vereinigen (Tabelle). Von diesem Ringsystem waren bislang nur 2-Oxo-Derivate bekannt.[2]



Die Reaktion vollzieht sich bei Raumtemperatur, wenn man kristallisiertes Benzonitriloxyd etwa in Benzaldehyd löst (Methode A). Bequemer ist es, das als Generator dienende Hydroxamsäurechlorid in der überschüssigen Carbonylverbindung oder deren ätherischer Lösung aufzunehmen und durch langsame Zugabe von Triäthylamin in Äther bei 0-20° das Nitriloxyd

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[1] R.Huisgen, Naturwiss.Rundschau 14, 43 (1961); Proc.Chem. Soc. im Druck.

[2] G.Beck, Chem.Ber. 84, 688 (1951).

Tabelle. 1.3-Additionen aromatischer Nitriloxyde an Carbonylverbindungen

R-CNO	R'-CO-R"		Metho-	1.3.4-Dioxazol (I)	
R =	R' =	R" =	de	Ausb.% d.Th.	Schmp.
C_6H_5	C_6H_5	H	A	45	41-42°
			B	55	"
C_6H_4	oCl-C_6H_4	H	B	84	61°
C_6H_5	α-Furyl	H	B	41	63-65°
C_6H_5	α-Pyridyl	H	C	75	Fl. *
C_6H_5	$CO_2C_2H_5$	H	D	67	Fl.
C_6H_5	CCl_3	H	E	44	43-44°
C_6H_5	CH_3-CO	CH_3	E	65	Fl.
C_6H_5	$CO_2C_2H_5$	CH_3	E	91	Fl. **
C_6H_5	$CO_2C_2H_5$	$CO_2C_2H_5$	B	75	Fl.***
pCl-C_6H_4	CH_3-CO	CH_3	E	81	41-42°
pCl-C_6H_4	$CO_2C_2H_5$	$CO_2C_2H_5$	B	38	46-47°
pNO_2-C_6H_4	$CO_2C_2H_5$	$CO_2C_2H_5$	B	71	78-80°

Schmp. * Pikrat 143-144°; ** Amid 110°; *** Diamid 214°

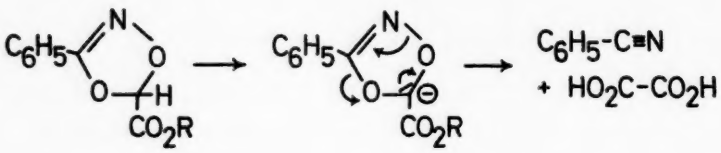
freizusetzen (Methode B). Hier, wie auch bei Methode C, langsamer Zugabe des Hydroxamsäurechlorids zur ätherischen Lösung der Carbonylverbindung und des tert.Amins, unterdrückt man mit einer niedrigen Stationärkonzentration des Nitriloxyds dessen störende Dimerisation zum Furoxan. Besonders basenempfindliche Carbonylverbindungen versetzt man entweder mit Hydroxamsäurechlorid und Triäthylamin aus 2 Tropftrichtern gleichzeitig (Methode D) oder man setzt zunächst aus dem Hydroxamsäurechlorid mit 1 Moläquiv. Amin bei -20° das Ni-

triloxyd frei, gibt die Carbonylkomponente hinzu und läßt langsam auf Raumtemperatur kommen (Methode E).

Im Gegensatz zu aromatischen Aldehyden treten aliphatische Aldehyde erst dann mit Nitriloxyden zusammen, wenn durch Chlor am Nachbarkohlenstoff oder durch benachbarte Carbonyl- bzw. Carbonesterfunktionen der elektrophile Charakter der Carbonylgruppe erhöht ist. Acetophenon, Äthylformiat und γ-Butyrolacton reagieren nicht.

Die 1.3.4-Dioxazole wurden durch Elementaranalyse, IR- und UV-Spektren sowie Abbaureaktionen charakterisiert. Das Ringsystem birgt eine Imidoester- und eine Acetalgruppe, läßt samit Säureempfindlichkeit voraussehen. Mit 2.4-Dinitrophonylhydrazin in alkoholisch-wäßriger Schwefelsäure lassen sich schon beim gelinden Erwärmen 90-98% der Carbonylverbindung festlegen; in der Lösung ist die Hydroxamsäure nachweisbar. Dagegen sind die Dioxazole, in denen R' oder R' und R" Carbonestergruppen bedeuten, recht hydrolysenbeständig.

Das Benzonitriloxyd-Addukt des Diacetyls läßt sich mit KOBr zu I (R = C_6H_5, R' = CO_2H, R" = CH_3) oxydieren und nach Veresterung mit Diazomethan in das gleiche Carbonamid überführen, das aus dem Addukt des Brenztraubenesters mit Ammoniak entsteht. Während die Addukte des Mesoxalesters (I, R' und R" = $CO_2C_2H_5$) mit Alkali nur an der Carbonestergruppe hydrolysiert werden, wird I (R = C_6H_5, R' = $CO_2C_2H_5$, R" = H) zu Benzonitril und Oxalsäure abgebaut:



Die von A.Quilico [3] studierten Additionen der Nitriloxyde an Alkene und Alkine sind ebenfalls als 1.3-Dipolare Additionen zu betrachten. Auch Nitrile,[4] Schiff-Basen [5] und Dipolarophile mit CS-Doppelbindung [6] vermögen das 1.3-System der Nitriloxyde unter Bildung von heterocyclischen Fünfringen aufzunehmen.

Wir danken der Deutschen Forschungsgemeinschaft und dem Fonds der Chemischen Industrie für die Förderung dieser und der folgenden Arbeit.

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[3] Letzte Mitteilung: N.Barbulescu, P.Grünanger, M.R.Langella und A.Quilico, Tetrahedron Letters 1961, 89.

[4] R.Huisgen, W.Mack und E.Anneser, nachstehend.

[5] R.Huisgen und W.Mack, unveröffentlicht.

[6] R.Huisgen, W.Mack und E.Anneser, Angew.Chem. 1961, im Druck.

Tetrahedron Letters No. 17, pp. 587-589, 1961. Pergamon Press Ltd. Printed in Great Britain.

DIE SYNTHESE VON 1.2.4-OXDIAZOLEN AUS NITRILOXYDEN UND NITRILEN

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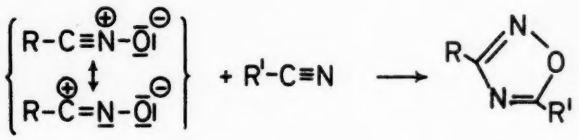
NITRILE lagern an der CN-Dreifachbindung das 1.3-System der Nitriloxyde unter Bildung von 1.2.4-Oxadiazolen an. Bei den vornehmlich mit Benzonitriloxyd ausgeführten Versuchen (Tabelle) erweisen sich aromatische Nitrile als reaktiv, nicht dagegen einfache aliphatische Nitrile. Erst unter dem Einfluß elektronenanziehender Substituenten erlangt die aliphatische Nitrilgruppe die Additionsbereitschaft.



Am einfachsten erzeugt man die Nitriloxyde in situ durch HCl-Abspaltung aus Hydroxamsäurechloriden mittels Base. Die verschiedenen möglichen Methoden dazu (C, D und E der Tabelle) wurden in der vorstehenden Arbeit [1] erörtert und sind

[1] R.Huisgen und W.Mack, Tetrahedron Letters vorstehend.

Tabelle. 1.3-Additionen der Nitriloxyde an Nitrile

R-CNO R =	R'-CN R' =	Methode	1.2.4-Oxadiazol Ausb.% d.Th.	Schmp.
C_6H_5	C_6H_5	A	56	107-109°
C_6H_5	C_6H_5	C	69	"
C_6H_5	ß-Pyridyl	C	56	118°
C_6H_5	Cl-CH_2	E	89	38°
C_6H_5	CH_3O-CH_2	E	31	Fl.
C_6H_5	C_6H_5O-CH_2	C	62	75-76°
C_6H_5	C_6H_5-CO	D	61	61-62°
C_6H_5	CH_3-CO	A	68	106°
C_6H_5	$CH_3(CN)C$- CH_3-CO-O	E	64	59-60°
C_6H_5	$CO_2C_2H_5$	D	71	53-53.5°
C_6H_5	CN	D	73	75-76°
p-Cl-C_6H_4	C_6H_5	C	>50	111-112°
$CO_2C_2H_5$	C_6H_5	C	gering	50°

sinngemäß auf die Umsetzung mit Nitrilen zu übertragen. Die Addition an Acetylcyanid - dessen Neigung zur Dimerisation stört - gelingt nur mit der ätherischen Lösung des reinen Benzonitriloxyds (Methode A). Die Dimerisation des Carbäthoxy-nitriloxyds zum Furoxanderivat läßt sich auch in verdünnter Lösung in Benzonitril nicht ausschalten.

Der Nitrilgruppe kommt offensichtlich eine höhere dipolarophile Aktivität zu als dem Carbonylsystem.[1] α-Ketonitrile nehmen das Nitriloxyd ausschließlich an der CN-Dreifach-

bindung auf.

Einige der 1.2.4-Oxadiazole sind literaturbekannt, andere wurden mit Präparaten identifiziert, die aus Benzamidoxim und den Carbonsäurechloriden R'-COCl synthetisiert wurden.

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THE STRUCTURE OF THE BROMODILACTONE FROM JACOBINE AND THE CONFORMATION OF THE LACTONE GROUP

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With regard to the evidence for the structures of the Senecio jacobaea alkaloids, considerable importance attached to the structure assigned to the dilactone [1,2,3] obtained by acid hydrolysis of jacobine. Because of the critical role of this derivative, an X-ray analysis of the bromodilactone of jacobine was initiated [4]. Subsequent chemical [5,6] and X-ray [7] evidence

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[1] R. Adams, M. Gianturco and B. L. van Duuren, J. Amer. Chem. Soc. 78, 3513 (1956).

[2] R. B. Bradbury and J. B. Willis, Aust. J. Chem. 9, 258 (1956).

[3] T. A. Geissman, Aust. J. Chem. 12, 247 (1959).

[4] J. C. Taylor, International Symposium on the Chemistry of Natural Products, Abstracts p. 43 (1960).

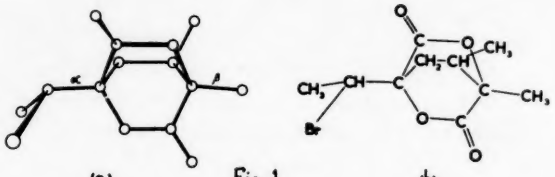
[5] R. B. Bradbury and S. Masamune, J. Amer. Chem. Soc. 81, 5201 (1959).

[6] S. Masamune, J. Amer. Chem. Soc. 82, 5253 (1960).

[7] J. Fridrichsons, A. McL. Mathieson and D. J. Sutor, Tetrahedron Letters No. 23, 35 (1960).

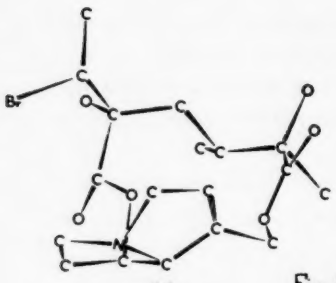
has provided a complete and detailed picture of the structure and absolute configuration of the parent compound, jacobine. The evidence presented here gives further confirmation regarding the jaconecic acid component of jacobine and also provides information on the conformation of the lactone group.

The needle-shaped crystals of the bromodilactone, $C_{10}H_{13}O_4Br$, belong to the monoclinic system, $\underline{a}$ = 8.70, $\underline{b}$ = 6.34, $\underline{c}$ = 10.44A, β = 98.2°, the space group being $P2_1$ with two molecules in the unit cell. Intensity data were collected at -150°C for the 0 - 4 layers about the $\underline{b}$ axis (947 measured reflections of 1125 possible). With zero-layer normal and first-layer generalised projections, phased first by the Br atoms and then with additional atoms as these were located, the spatial location of all atoms (except H) constituting the molecule was achieved in a few cycles. The atomic coordinates were then refined by least-squares procedures using the complete set of data. At this stage, the overall reliability index is 0.14.

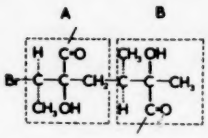


(a) Fig. 1 (b)

The molecular skeleton as viewed at a slight angle to the $\underline{b}$ axis is shown in Fig. 1a (correct absolute configuration) and the conventional formulation in Fig. 1b. The structure is in complete agreement with that proposed by Geissman [3] and is in accord with the structure of jacobine [5]. The relative configurations of the four asymmetric centres in the dilactone are in agreement with those in the jaconecic acid component of jacobine [6, 7] Fig. 2a, and by reference to the absolute configuration of jacobine defined by chemical and X-ray evidence were placed on an absolute basis, Fig. 1a. The antipodal relationship, noted earlier [7], between the A and B units of the jaconecic acid component in jacobine bromhydrin, Fig. 2b, is a concomitant of the formation of the dilactone from jacobine.



(a)



(b)

Fig. 2

With regard to the structure of the dilactone, the bicyclic part is composed of the backbone carbon chain and the two lactone functions, the small difference between the — C — C — and — C — O — bond lengths causing a deviation from collinearity of the bonds α and β, Fig. 1a. The lactone group exhibit two points of more general interest, each group — C — C(=O) — O — C — being coplanar within the accuracy of the analysis and the bonds y longer than the bonds x by approximately 0.1 Å. These conditions were noted first with respect to the γ-lactone group in himbacine hydrobromide [8] and have received further support in the analysis of iso-iridomyrmecin [9]. Combined with the evidence for the two δ-lactone groups in the present analysis, these factors would appear to be sufficiently consistent to be regarded as characteristic of lactone groups.

The coplanarity of the lactone group brings it into accord with the known characteristics of the related amide [10] and ester [11] groups. Conditions of this type constitute further useful conformational restrictions in assessing the validity of molecular models.

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[8] J. Fridrichsons and A. McL. Mathieson, Acta Cryst. in press (1961).

[9] J. F. McConnell and B. Schoenborn, Private communication.

[10] L. Pauling and R. B. Corey, J. Amer. Chem. Soc. 74, 3964 (1952).

[11] a) G. W. Wheland, Resonance in Organic Chemistry. J. Wiley and Sons, New York (1955).

b) M. L. Bender, Chem. Revs. 60, 53 (1960).

c) Supporting evidence for coplanarity of ester groups is evident in the structure of jacobine bromhydrin Fig. 2a.

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ON THE HOMOLOGATION OF STABLE CARBONIUM IONS

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(Received 6 September 1961)

THE nucleophilic character of diazomethane suggests that it should react with carbonium ions as shown in the following generalized equation.

$$\underset{\text{I}}{R_2C}^{+} \longrightarrow R_2C\text{-}CH_2N_2^{+} \longrightarrow \underset{\text{II}}{R_2C\text{-}CH_2}^{+} \longrightarrow \text{Products}$$

From this equation one might anticipate that the carbonium ion I must be of more than transitory existence, i.e. a "stable" carbonium ion, and that since one is generating a primary carbonium ion of the type II, Wagner-Meerwein rearrangements will ensue. To test the feasibility of this reaction[1] we have examined the reaction of diazomethane with three stable carbonium ions, xanthylium (IIIa), thiaxanthylium (IIIb), and N-methylacridinium (IIIc) ions These were chosen since the homologated carbonium ions IV if formed should rearrange to the corresponding dibenz [b,f] oxepin (Va),[5] dibenzo [b,f]

[1] The formation of aziridinium salts from the reaction of iminium salts with diazomethane[2] may be considered to be an example of this reaction

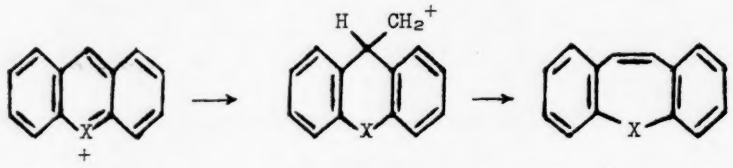
[2] N.J. Leonard and K. Jann, J.Amer.Chem.Soc. 82, 6418 (1960).

[3] E.D. Bergmann and M. Rabinovitz, J.Org.Chem. 25, 827 (1960).

[4] E.D. Bergmann and M. Rabinovitz, J.Org.Chem. 25, 828 (1960).

[5] F.L. Anet and P.M.G. Bavin, Canad.J.Chem. 35, 1084 (1957).

thiepin (Vb)[4] and N-methyldibenzo [b,f] azepin (Vc).[6]



III a) X = O
b) X = S
c) X = NCH_3

IV a) X = O
b) X = S
c) X = NCH_3

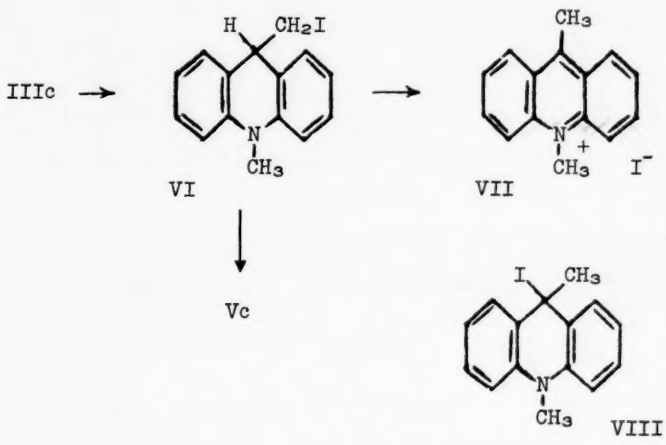
V a) X = O
b) X = S
c) X = NCH_3

The reaction of xanthylium perchlorate (IIIa) with ethereal diazomethane proceeded briskly at 0°, accompanied by nitrogen evolution and the dissolving of the salt, affording after chromatography a 61% yield of the expected dibenz [b,f] oxepin (Va), m.p. 108-109° (Found: C, 86.49; H, 5.21), reported,[7] m.p. 111°, possessing the appropriate U.V.[5] and I.R. spectra.

Similarly, the reaction of thiaxanthylium perchlorate (IIIb) with diazomethane at 0° afforded after chromatography a 22% yield of dibenzo [b,f] thiepin (vb), m.p. 86-87° (Found: C, 79.80; H, 4.88, S, 15.25), reported,[4] m.p. 89-90°, possessing the correct U.V. and I.R. spectra.[4]

Since the very insoluble N-methyl acridinium perchlorate failed to react with ethereal diazomethane, the reaction of N-methyl acridinium iodide (IIIc) with diazomethane was investigated, a slow (12 hr) reaction occurring which afforded a low yield (less than 10%) of N-methyldibenzo [b,f] azepin (Vc), bright yellow needles, m.p. 142-143° (Found: C, 86.82; H, 6.49; N, 6.80), reported,[6] m.p. 143-144°. The main product from this reaction was a colorless compound, needles, m.p. 115° (d), isolated in 50% yield, whose structure is assigned as VI (Found: C, 54.05; H, 4.11; N, 3.88; I, 38.26. Calc. for $C_{15}H_{14}NI$: C, 53.75; H, 4.21; N, 4.18; I, 37.87). On heating to its

[6] R. Huisgen, E. Laschtuvka, and F. Bayerlein, Chem.Ber. 93, 392 (1960).
[7] R.H.F. Manske and A.E. Ledingham, J.Amer.Chem.Soc. 72, 4799 (1950).



melting point or on merely standing at room temperature in methanol VI rearranged by a 1-2 hydrogen shift to form 9,10-dimethyl acridinium iodide (VII), m.p. 255° (d) (Found: C, 53.66; H, 4.17; N, 4.03; I, 37.98), identified by comparison with an authentic sample. In contrast VI reacted with silver perchlorate in ether to afford by an aryl shift N-methyl dibenzo [b,f] azepin (Vc) (29%) together with a 9% yield of VII, the isolation of the azepin eliminating the alternative structure VIII.

The formation of VI in the reaction of acridine methiodide with diazomethane may be interpreted as an initial attack by diazomethane, affording the ion IVc which is largely captured by the nucleophilic iodide ion to afford VI, a small percentage of IVc rearranging via an aryl shift to afford the azepin Vc. On the other hand the perchlorates of IIIa and IIIb react with diazomethane forming, respectively, IVa and IVb which in the absence of a nucleophilic ion rearrange to the corresponding oxepin (Va) and thiepin (Vb). On reflection one may envisage a number of interesting aspects of this reaction, the more titillating of which are being actively pursued.

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STUDIES ON THE MODE OF INCORPORATION OF MEVALONIC ACID INTO ERGOT ALKALOIDS

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(Received 31 August 1961)

RECENT reports[1,2,3] have shown (2-^{14}C) DL-mevalonic acid to be an active precursor of lysergic acid and clavine type alkaloids. Degradation studies of the radioactive agroclavine and elymoclavine isolated from C. purpurea fed with (2-^{14}C) DL-mevalonic by Birch et al.[1] have shown that about 30% of the radioactivity was present at the $C_{(17)}$ in agroclavine and about 90% in the case of elymoclavine*. These experiments supplemented with those concerned with the incorporation of (1-^{14}C) and (2-^{14}C) acetic acid are consistent with the incorporation of mevalonate but do not present a clear picture of the distribution of the radioactive carbon of mevalonic acid in the ergot alkaloids. Further speculation respecting the mode of incorporation of mevalonic acid requires a more detailed picture.

Groger et al.[2] have shown that the specific percentage incorporation of (2-^{14}C), (2-T), (4-T) DL-mevalonic acids into the ergot alkaloids are

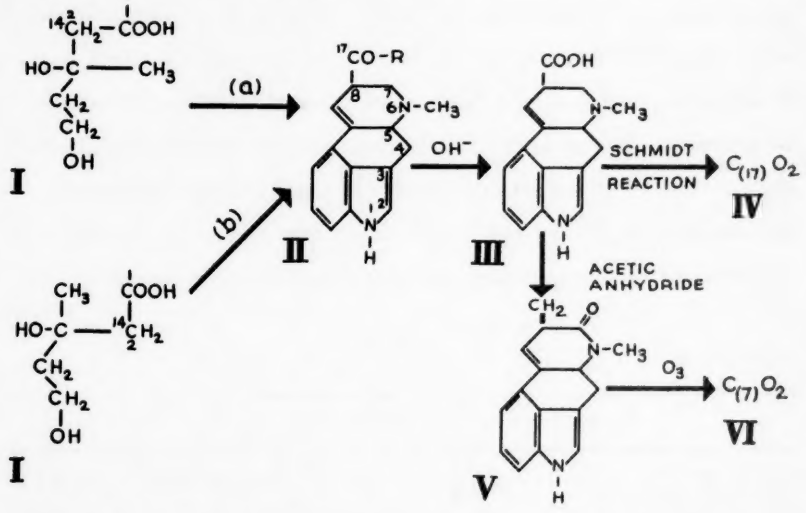
* A very recent personal communication from Dr. Birch indicates that subsequent data has revealed 90% of the radioactivity (2-^{14}C) mevalonic lactone at $C_{(17)}$ for agroclavine as well.

1 A.J. Birch, D.J. McLoughlin and H. Smith, Tetrahedron Letters No. 7, 1 (1960).

2 K. Mothes, H. Simon, H.G. Floss and F. Weygand, Z. Naturf. 15b, 141 (1960).

3 E.H. Taylor and E. Ramstad, Nature,Lond. 188, 494 (1960).

very close to each other suggesting the incorporation of mevalonic acid as a unit. Assuming therefore, the incorporation of mevalonic acid as a unit with the loss of the carboxyl carbon prior or subsequent to incorporation, the (2-^{14}C) of the (2-^{14}C) DL-mevalonic acid should appear at $C_{(17)}$ (I $\xrightarrow{(a)}$ II) or at $C_{(7)}$ (I $\xrightarrow{(b)}$ II) of the ergot alkaloids. The distribution of the (2-^{14}C) between the $C_{(17)}$ and $C_{(7)}$ might also occur to some degree and the randomization of this radioactive carbon is conceivable either prior to or after incorporation.



In order that more definite information respecting the relative degree of localization of the (2-^{14}C) carbon of mevalonate might be obtained a degradation was devised whereby the $C_{(7)}$ and $C_{(17)}$ of lysergic acid was isolated individually as carbon dioxide. The radioactive ergosine (II, R=peptide side chain of ergosine) isolated from the cultures of Claviceps purpurea, PRL 1578, to which had been added 200 μc of (2-^{14}C) DL-mevalonic acid (I), was diluted with an appropriate quantity of unlabelled ergosine

and was converted[4] to lysergic acid (III). The Schmidt reaction of (III) afforded the $C_{(17)}$ as carbon dioxide (IV). Lysergic acid treated[5] with acetic anhydride yielded the lactam (V) which yielded formaldehyde on ozonization. The formaldehyde so obtained was converted into carbon dioxide (VI) derived from the $C_{(7)}$ of lysergic acid.

Preliminary experiments were also carried out concerning the pathway of incorporation of mevalonate. Assuming a pathway similar to cholesterol[6], (1-^{14}C) DL-mevalonic acid was added to a clavine producing strain of C. purpurea to obtain data respecting the fate of the carboxyl group of mevalonic acid. The inhibitory effect of unlabelled isopentenylpyrophosphate and dimethylallylpyrophosphate on the incorporation of (2-^{14}C) mevalonate was also investigated. (Dimethylallylpyrophosphate was prepared from dimethylallyl alcohol obtained by the reduction of dimethylacrylic acid with lithium aluminium hydride by phosphorylation[7] in a manner similar to that reported by Yuan and Bloch[8] for the preparation of isopentenylpyrophosphate.)

Table 1

	Lysergic acid	Lactam	$C_{(17)}O_2$	$C_{(7)}O_2$
d.p.m./mM	2.38×10^4	2.38×10^4	2.39×10^4	1.51×10^3
Recovery %			100.4	6.3

[4] W.A. Jacobs and L.C. Craig, J.Biol.Chem. 104, 547 (1934).

[5] A. Stoll, A. Hofmann and F. Troxler, Helv.Chim.Acta 32, 506 (1948).

[6] T.T. Tchen, in Metabolic Pathways (Edited by D.M. Greenberg) Vol. I, p.392. Academic Press, New York (1960).

[7] R.M. Baxter, S.I. Kandel and K.L. Tam, unpublished data.

[8] C. Yuan and K. Bloch, J.Biol.Chem. 234, 2605 (1959).

In Table 1 are shown the specific activities of lysergic acid, the lactam and its degradation products ($C_{(17)}O_2$ and $C_{(7)}O_2$). These data indicate that nearly all the activity is localized in the carboxyl carbon $C_{(17)}$ of lysergic acid with only a small percentage in the $C_{(7)}$ and constitute strong evidence that the (2-^{14}C) of mevalonic acid becomes the $C_{(17)}$ of lysergic acid ($I \xrightarrow{(a)} II$). It would appear that the randomization of mevalonate occurs to a small extent. Whether this occurs during its conversion to more immediate precursors (isopentenylpyrophosphate ⟶ dimethylallylpyrophosphate) or at a later stage remains to be established.

Table 2

Additives		Specific activity c.p.m./mM	Inhibition %
^{14}C	Unlabelled		
(1-^{14}C) DL-Mevalonic acid (2 μc)	-	-	
(2-^{14}C) DL-Mevalonic acid (0.73 μc)	-	7.12 x 10^5	
(2-^{14}C) DL-Mevalonic acid (0.73 μc)	IsPP*, 0.500 mg	7.0 x 10^5	-
(2-^{14}C) DL-Mevalonic acid (0.73 μc)	DMPP**, 0.500 mg	6.6 x 10^5	7.3
(2-^{14}C) DL-Mevalonic acid (0.73 μc)	DMPP**, 2.5 mg	4.47 x 10^5	38.6
(2-^{14}C) DL-Mevalonic acid (0.73 μc)	-	4.73 x 10^5	
(2-^{14}C) DL-Mevalonic acid (0.73 μc)	IsPP*, 0.642 mg	3.73 x 10^5	21
(2-^{14}C) DL-Mevalonic acid (0.73 μc)	IsPP*, 1.284 mg	2.83 x 10^5	32
(2-^{14}C) DL-Mevalonic acid (0.73 μc)	DMPP**, 0.642 mg	2.40 x 10^5	50

* IsPP = Isopentenylpyrophosphate cyclohexylammonium salt.
** DMPP = Dimethylallylpyrophosphate cyclohexylammonium salt.

The data in Table 2 indicate that none of the radioactivity from (1-^{14}C) DL-mevalonate was incorporated into the alkaloids isolated (pyroclavine and festuclavine) and that both of the assumed precursors inhibit the incorporation of (2-^{14}C) DL-mevalonate. Since it is not possible to assume with complete certainty that the pool size of the assumed precursors and that the rate of formation of the alkaloids are the same in each case it is not possible to unequivocably state which of the two mevalonic acid metabolites is the more immediate precursor. The randomization of mevalonate however indicates a preference for the dimethylallylpyrophosphate. The inhibitory effect of isopentenylpyrophosphate would be an indirect one since it is converted into dimethylallylpyrophosphate, a fact which is consistent with published data[9]. The incorporation of deuterated isopentenylpyrophosphate into clavine alkaloids was reported[10] during the course of this work. It is anticipated that more direct information will be obtained from experiments which are in progress using labelled dimethylallylpyrophosphate.

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[9] B.W. Agranoff, H. Eggerer, U. Henning and F. Lynen, J.Biol.Chem. 235, 326 (1960).

[10] H. Plieninger, R. Fischer, G. Keilich and H.D. Orth, Ann. 642, 213 (1961).

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THE REDUCTION OF STEROIDAL 3-KETO-1,4-DIENES

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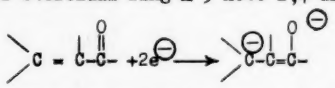
THE concept[1,2] of the two electron additions to α, β unsaturated ketones undergoing reduction by dissolving metals in ammonia, has led to some novel reduction products of steroidal ring A-3-keto-1,4-dienes,



by utilization of the reactive carbanion beta to the carbonyl generated during the reduction of these steroids.

The reduction of prednisone BMD[3] (I) with lithium and ammonia leads in good yield to a 9//10 seco product (II), m.p. 235-239°; $[\alpha]_D$ -5; λ_{max}^{MeOH} 280 mμ, ϵ = 2600; $\lambda_{infl.}^{MeOH}$ 285 mμ, ϵ = 2445, by a concerted two electron addition process.

Analogous phenolic 9//10 seco compounds of this type have been prepared by the pyrolysis of ring A unsaturated C.3-ketones.[4] In a similar manner, lithium and ammonia reduction of 1,4-androstadiene-3,11,17-trione affords the 9//10 seco product, 3-hydroxy-9//seco-1,3,5(10) androstatriene-11,17-dione, m.p. 210-213°; $[\alpha]_D$ + 80; ϵ_{max}^{MeOH} 280 mμ, = 2370.[5]

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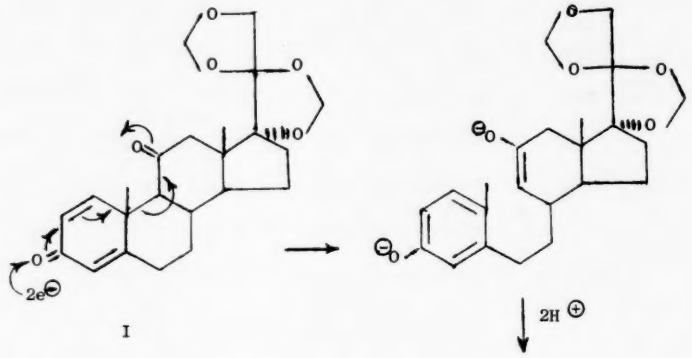
[1] A.J. Birch, Quart.Rev. 4, 69 (1950).

[2] D.H.R. Barton and C.R. Robinson, J.Chem.Soc. 3045 (1954).

[3] R.E. Beyler, R.M. Moriarty, Frances Hoffman and L.H. Sarett, J.Amer.Chem.Soc. 80, 1517 (1958).

[4] B.J. Magerlein and J.A. Hogg, Tetrahedron 2, 80 (1958).



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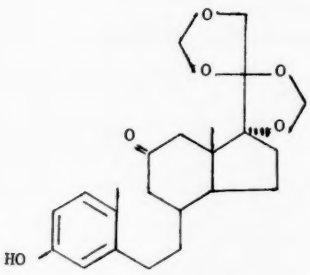
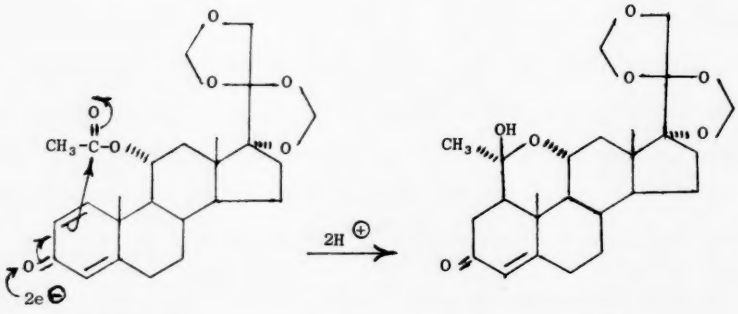


II



III IV

[5] These physical constants are in agreement with the published values of ref. 4. Satisfactory analyses have been obtained for all new compounds herein described. Rotations are in chloroform and the melting points are uncorrected.

Reduction with lithium and ammonia of ring A-3-keto-1,4-dienes having a neighboring 11α-acetoxy substituent leads to intramolecular acylation of the incipient β-carbanion generated at C.1. Thus the controlled lithium and ammonia reduction of 11α-acetoxy-17α, 20:20, 21-bismethylenedioxy-1,4-pregnadiene-3-one (III); m.p. 199-203°; λ_{max}^{MeOH} 245 mμ, ε = 15,000; λ_{max}^{Nujol} 5.78, 6.0, 6.15, 6.25, 8.5μ leads to a 1,2-dihydro-1-acetyl derivative (IV),[6] m.p. 210-213°; $[\alpha]_D$ - 8.0; λ_{max}^{MeOH} 242 mμ, ε = 10,800; λ_{max}^{Nujol} 3.05, 6.0, 6.15, 9.15μ.

The 1-acetyl derivative (IV) exists as the cyclic hemiketal tautomer as evidenced by the absence of saturated carbonyl absorption and the presence of hydroxyl absorption in the infra-red spectrum.

The cyclic hemiketal structure implies that the configuration of the masked 1-acetyl group is β-oriented. This allows the preferred accommodation of the fused tetrahydropyran ring in the more stable chair conformation.

The configuration at the hemiketal carbon C.1 presumably has the larger methyl substituent equatorial and α-oriented.

Acknowledgement - We thank the Schering Corporation, Bloomfield, New Jersey, for support of this work.

[6] A similar intramolecular acylation of a carbanion produced during Birch reduction of 11β-acetoxy-estrone-3-methyl ether has been reported; see B.J. Magerlein and J.A. Hogg, J.Amer.Chem.Soc. 80, 2223 (1955). The intramolecular discharge by alkylation of a beta-carbanion generated by lithium and ammonia reduction of an eneone has been recently reported; see G. Stork and J. Tsuji, Ibid. 83, 2783 (1961).

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OPTICALLY ACTIVE 3,3′-BITHIENYLS

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A STUDY of restricted rotation in the bithienyl series, which should give valuable information about the geometric and electronic properties of such compounds, has hitherto been very difficult to undertake owing to difficulties involved in the synthesis of such compounds. Some years ago Nord et al. [1,2] investigated two sterically hindered 2- and 3-phenylthiophenes, which they synthesized from the corresponding halides via the Ullman reaction, and which they resolved into optical antipodes. They also prepared some 3,3′-bithienyls[3] through the Ullman reaction, but it remains difficult to obtain such compounds by this method.

The reaction of 3-thienyllithium derivatives, obtained through low-temperature halogen-metal interconversion of bromosubstituted thiophenes[4,5] with n-butyllithium, with cupric chloride,[6] provides a new route to 3,3′-bithienyls. Sterically hindered 3,3′-bithienyls are then easily available

[1] L.J. Owen and F.F. Nord, J.Org.Chem. 16, 1864 (1951).

[2] G.N. Jean, J.Org.Chem. 21, 419 (1956).

[3] G.N. Jean and F.F. Nord, J.Org.Chem. 20, 1363 (1955).

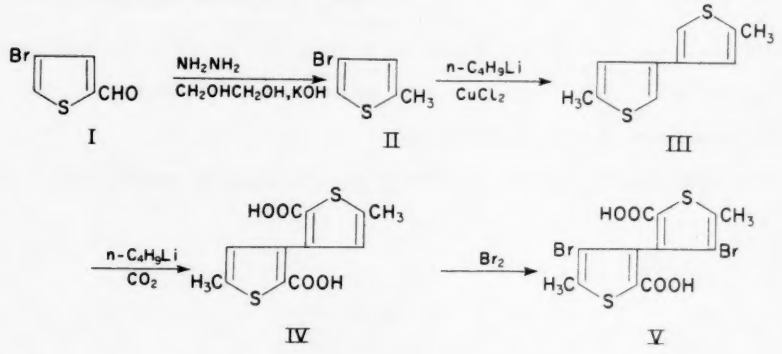
[4] S. Gronowitz, Arkiv Kemi 13, 295 (1958).

[5] S. Gronowitz, P. Moses, A.-B. Hörnfeldt and R. Håkansson, Arkiv Kemi 17, 165 (1961).

[6] S. Gronowitz and H.O. Karlsson, Arkiv Kemi 17, 89 (1960).

through metalation[7], halogen-metal interconversion[8] and other substitution reactions with the 3,3′-bithienyls so obtained.

As a first example, we have prepared 2,2′-dicarboxy-4,4′-dibromo-5,5′-dimethyl-3,3′-bithienyl in the following way: 4-bromo-2-thiophenealdehyde (I) was converted into 4-bromo-2-methylthiophene (II) through the Wolff-Kishner reduction. B.p. 61-62°/11 mm Hg, n_D^{20} = 1.5725 (Found: C, 34.13; H, 2.93. Calc. for C_5H_5BrS: C, 33.91; H, 2.84%). Yield 84%.



Treatment of II with n-butyllithium and $CuCl_2$ at -70° yielded 5,5′-dimethyl-3,3′-bithienyl (III), m.p. 135-136° (Found: C, 62.01; H, 5.23; S, 32.90. Calc. for $C_{10}H_{10}S_2$: C, 61.81; H, 5.19; S, 33.00%). Yield 23%. Refluxing III with excess n-butyllithium for 4 hr followed by carbonation with dry ice yielded 2,2′-dicarboxy-5,5′-dimethyl-3,3′-bithienyl (IV), m.p. 254-257° dec. (Found: C, 50.92; H, 3.74. Calc. for $C_{12}H_{10}O_2S_2$: C, 51.05; H, 3.57). Yield 60%. Upon treatment with excess bromine this gave 2,2′-dicarboxy-4,4′-dibromo-5,5′-dimethyl-3,3′-bithienyl (V) m.p. 312-313° dec. (Found: C, 32.64; H, 1.94; Br, 36.53. Calc. for $C_{12}H_8Br_2O_2S_2$: C, 32.74,

[7] S. Gronowitz and H.O. Karlsson, to be published.

[8] S. Gronowitz, to be published.

H, 1.83; Br, 36.32%). Yield 80%. III was chosen instead of 3,3′-bithienyl as the metalation of the latter compound with excess n-butyllithium gives a mixture of about equal amounts of 2,2 -dicarboxy-3,3′-bithienyl and 5,5′-dicarboxy-3,3′-bithienyl upon carbonation.[7]

Crystallization of the cinchonine salt of V from aqueous ethanol gave well-defined crystals $[\alpha]_D^{25} = -152°$ (c, 1.10 chloroform). Through decomposition of this salt with hydrochloric acid optically active V was obtained, $[\alpha]_D^{25} = +43°$ (c, 0.51 acetone), $[\alpha]_D^{25} = -57°$, (c, 1.28 chloroform) $[\alpha]_D^{25} = -195°$ (c, 1.14, 0.1-N NaOH). As far as we know this is the first time the resolution of 3,3′-bithienyls has been demonstrated. Further work on the atropisomerism of bithienyls is in progress.

A grant from Hierta-Retzius foundation is gratefully acknowledged.

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ASYMMETRIC SYNTHESIS AND ABSOLUTE CONFIGURATION OF SOME SULPHOXIDES

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(Received 13 September 1961)

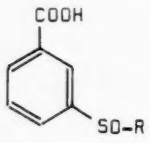
THE partial asymmetric synthesis of sulphoxides (I) C_6H_5-SO-Alk,[1] by oxidation of the sulphides with (1S)(+) percamphoric acid (IV),[2] has been previously described. The investigation has now been extended to the corresponding meta- and ortho-carboxylated derivatives (II) and (III), whose absolute configurations have been determined.

The optically active sulphoxides (II) and (III) have been prepared by oxidation of methyl esters of the sulphides with (1S)(+) perchamphoric acid (IV) and (S)(+) perhydratropic acid (V) ($CHCl_3$, -5°), followed by saponification. The compound (III) has also been prepared by the alternative route of esterification of the sulphide with optically active alcohols [(R)(-) menthol (VI), (R)(+) methyl-mesityl-carbinol (VII), (S)(-) methyl-α-naphtyl-carbi-

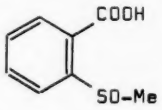
[1] F. Montanari et al., Gazz.Chim.Ital. 90, 739 (1960); Ricerca Sci. 30, 746 (1960). Other works on the same subject have been published at the same time by K. Balenović et al., Tetrahedron Letters No. 6, 20 (1960); Chem. and Ind. 469 (1961).

[2] Configuration nomenclature after R. S. Cahn, C. K. Ingold and V. Prelog, Experientia 12, 81 (1956).

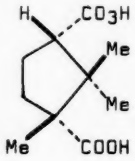
nol (VIII)], followed by oxidation with perbenzoic acid ($CHCl_3$, -5°) and saponification.



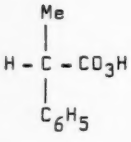
II : R = Me, Et, i-Pr, t-But



III



IV



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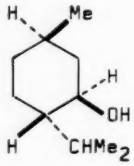

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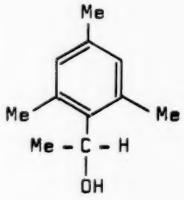
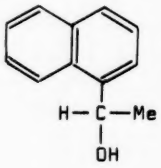


VII



VIII

The results, reported in Table 1, are interpreted as follows. The oxidation of sulphides to sulphoxides takes place through an electrophilic attack of the peracid in a perpendicular direction to the sulphide molecule.[3]

Indicating with S, M, L the ligands of small, medium and large size respectively,[4] surrounding the CO_3H group in molecules

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[3] C. G. Overberger and R. W. Cumming, J.Amer.Chem.Soc. 75, 4250 (1953); G. Modena et al., Gazz.Chim.Ital. 89, 834 (1959) and following papers. A tetrahedric direction of attack does not effect our considerations.

[4] V. Prelog, Bull.Soc.Chim. 986 (1955); D. J. Cram and F. A. Abd Elhafez, J.Amer.Chem.Soc. 74, 5828 (1952).

Table 1

Peracid or alcohol		Sulphoxide [a]					
Formula	Abs.Conf.n	Formula	R	$[\alpha]_D^{20°}$ found	$[\alpha]_D^{20°}$ theor.	Optical yield	Abs.Conf.n
IV	S	II	Me	+4°,9	±114°[b,e]	4,3	R
V	S	II	Me	+3°,1		2,7	R
IV	S	II	Et	+2°,5	±202°[c,e]	1,2	R
V	S	II	Et	+2°,1		1,0	R
IV	S	II	i-Pr	-0°,7	±184°[c,f]	0,4	S
V	S	II	i-Pr	-0°,2		0,1	S
IV	S	II	t-But	-3°,8	±156°[c,g]	2,4	S
V	S	II	t-But	-2°,5		1,6	S
IV	S	III	-	+4°,6		2,0	R
V	S	III	-	+3°,0		1,3	R
VI	R	III	-	-14°,0	±227°,5[d,h]	6,2	S
VII	R	III	-	-46°,6		20,5	S
VIII	S	III	-	+20°,2		8,9	R

[a] Average yields : 90-95% on the sulphide.

[b] MeOH [c] $CHCl_3$ [d] EtOH

[e] P. W. B. Harrison, J. Kenyon and H. Phillips, J.Chem.Soc.,2079 (1926).

[f] M.p. 114°-5°; found : C, 56,39; H, 5,78; S, 14,94. $C_{10}H_{12}O_3S$ requires : C, 56,58; H, 5,70; S, 15,10.

[g] M.p. 148° ; found : C, 58,43; H, 6,31; S, 14,01. $C_{11}H_{14}O_3S$ requires : C, 58,38; H, 6,24; S, 14,17.

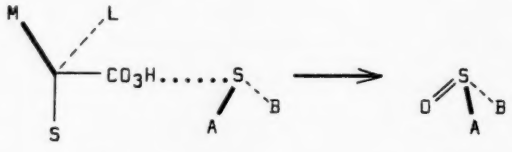
[h] M.p. 186° ; found : C, 52,16; H, 4,42. $C_8H_8O_3S$ requires : C, 52,2; H, 4,35.

(I) to (V), and with A-S-B the sulphide molecules, the most probable conformations in the reaction state are the staggered ones (a) and (b). If A>B, (a) is more favoured since the larger group A is placed in the less hindered position. The yield of the asymmetric synthesis is a function of the predominance of the reaction (a) over (b) and must augment with increasing difference in size among S, M, L, and, for the same oxidizing agent, between A and B. The latter difference must be more relevant in the neighbourhood of sulphur than further away.

In the series (II) all the terms present plain[5] rotatory dispersion curves, which, for equal sign, are almost superimposed in the region 600-300 mμ:[6] this suggests equal absolute configurations.

By oxidation with peracids (IV) and (V) [absolute configuration (S)] , dextro-enantiomers prevail when R = Me, Et, levo- when R = i-Pr, t-But. Being the larger term in the neighbourhood of sulphur the phenyl in the former case, and the alkyl group in the latter, the absolute configuration of sulphoxides (II) must be (S) and (R) respectively. The maximum yield of asymmetric synthesis is in fact observed when R = Me and respectively t-But, as expected when the difference in size between the groups bonded to sulphur is the greatest.

(a)

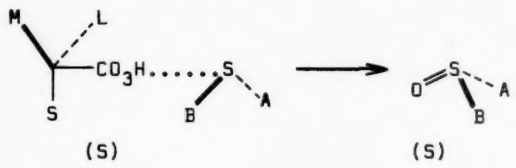


(S) (R)

[5] C. Djerassi and W. Klyne, Proc.Chem.Soc. 55 (1957).

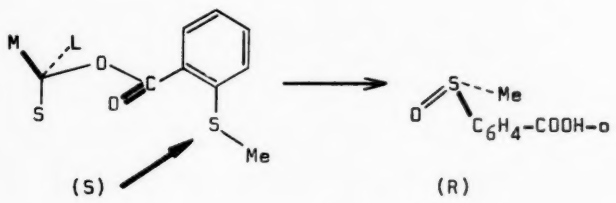
[6] We are greatly indebted to Prof. W. Klyne (London) for the determination of the rotatory dispersion curves. For RD curves of sulphoxides see also : W. Klyne, J. Day and A. Kyaer, Acta Chem.Scand. 14, 215 (1960).

(b)



(S) (S)

(c)



(S) (R)

The asymmetric synthesis of (III), involving oxidation of optically active esters of the sulphide, can be represented as in (c) (here S, M, L are the small, medium and large groups of the optically active alcohols). The most probable conformation of the sulphide is that where the carbonylic oxygen is placed in the less hindered region, i.e. between S and M.[7] Then, the largest group L shields one of the directions of attack of the peroxide [below the plane in (c)]. This fact agrees with higher optical yields obtained in this way.

The absolute configurations attributed to the enantiomers (III) according to (c) correspond to those derived from (a) and (b).

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[7] Other effects, for instance C=O...H-C interaction, may intervene; however, in the cases here examined, the conclusions are not significantly affected.

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cyclo-DIAZOMETHAN [1]

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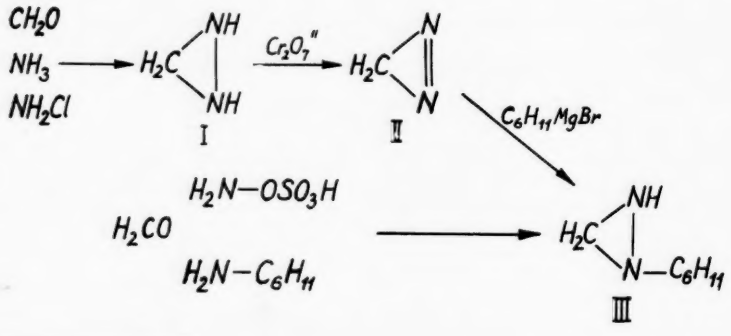
Berlin-Adlershof

(Received 6 September 1961)

Die kürzlich in mehreren Arbeitskreisen aufgefundene Diaziridin-Synthese aus Ketonen [2] kann auf Aldehyde übertragen werden. Zugabe von Formaldehyd zu Lösungen von Chloramin in methanolischem Ammoniak führt zur Bildung von Diaziridin (I). I kondensiert mit weiterem Formaldehyd; Hydrolyse mit Säuren setzt I wieder in Freiheit. Die Lösungen von I in Säuren zeigen das für Diaziridine charakteristische Oxydationsvermögen gegenüber Jodid [2]. Erwärmt man schwefelsaure Lösungen von I mit Bichromat, so entweicht ein Gas, das mit flüssiger Luft zu einer farblosen Flüssigkeit kondensiert werden kann. In dieser Verbindung erkannten wir das cyclische Isomere des Diazomethans (II).



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[1] Cyclische Diazoverbindungen, II. Mitteil., I. Mitteil.: E. Schmitz und R. Ohme, Chem.Ber. 94, 2166 (1961).

[2] Literatur: L.c. [1].

961

Katalytische Hydrierung von II führt zu einem Gemisch von Ammoniak und Methylamin. Während II durch Mineralsäuren und starkes Alkali nicht verändert wird, werden Grignardverbindungen leicht angelagert. Die Umsetzung mit Cyclohexyl-magnesiumbromid beweist die Dreiringstruktur. Es bildet sich dabei 1-Cyclohexyl-diaziridin (III, Kp_{16} 82°, n_D^{20} 1.4831, gef. für $C_7H_{14}N_2$: C 66.46 H 11.18 N 22.14). III kann hydrolytisch zu Formaldehyd und Cyclohexylhydrazin gespalten werden. Bei Einwirkung von angesäuerter Kaliumjodid-Lösung auf III werden zwei Äquivalente Jod freigesetzt; dabei entstehen durch N-N-Spaltung Cyclohexylamin und Ammoniak neben Formaldehyd. Beide Spaltungsreaktionen von III sind für Diaziridine typische Reaktionen [2, 3]. Auch die Synthese von III läßt sich auf einem für Diaziridine angegebenen Wege [2, 4] durchführen: Man erhält III aus Formaldehyd, Cyclohexylamin und Hydroxylamin-O-sulfonsäure.

cyclo-Diazomethan (II) ist selbst bei -40° explosiv; seine Lösungen sind dagegen bei Raumtemperatur stabil. Das UV-Spektrum von II in Methanol zeigt ein Maximum bei 321 mμ, wodurch sich II deutlich vom Diazomethan ($\lambda_{Max.}$ 412 mμ [5]) und vom Isodiazomethan ($\lambda_{Max.}$ 247 mμ [6]) unterscheidet, während Azomethan bei 343 mμ absorbiert [5].

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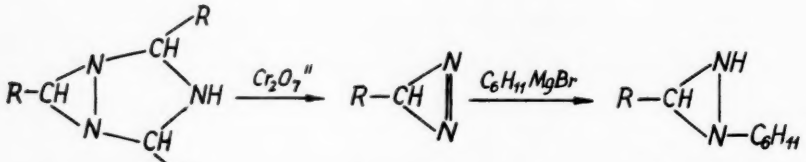
3 E. Schmitz und D. Habisch, Chem.Ber., im Druck.

4 H.J. Abendroth, Angew.Chem. 73, 67 (1961).

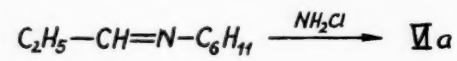
5 G. Kortüm, Z.physik.Chem. (B) 50, 361 (1941).

6 E. Müller und D. Ludsteck, Chem.Ber. 87, 1887 (1954).

Höhere Aldehyde geben analoge Verbindungen. Beispielsweise isoliert man als Einwirkungsprodukt von Chloramin und Ammoniak auf Butyraldehyd das Diaziridin-Derivat IV (Fp.86°). IV wurde durch Bichromat-Schwefelsäure zur cyclischen Diazoverbindung V oxydiert (Kp. 60-70°), die beim Versuch der Redestillation heftig explodierte. Umsetzung von V mit Cyclohexyl-magnesiumbromid ergab das Diaziridin-Derivat VI. Die gleiche Reaktionsfolge



IV: R=C_3H_7 V: R=C_3H_7 VI: R=C_3H_7
IVa: R=C_2H_5 Va: R=C_2H_5 VIa: R=C_2H_5



führte vom Propionaldehyd über das Diaziridin-Derivat IVa (Fp. 105°) und das 1-cyclo-Diazopropan (Va) zum 1-Cyclohexyl-3-äthyl-diaziridin (VIa). VIa (Fp.28°) wurde zum Vergleich aus Propyliden-cyclohexylamin und Chloramin synthetisiert [3].

Durch die Herstellung des cyclo-Diazomethans (II) ist das lange umstrittene Strukturproblem des Diazomethans auch chemisch gelöst.

Tetrahedron Letters No. 18, pp. 615-623, 1961. Pergamon Press Ltd. Printed in Great Britain.

CONSTITUTION OF THE CUCURBITACINS[1,2]

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Daniel Sieff Research Institute, the Weizmann Institute of Science, Rehovoth, Israel

(Received 26 September 1961)

CUCURBITACINS are the various bitter highly toxic principles occurring in the Cucurbitaceae. Some have been investigated for their anti-tumor activity.[4]

Based on dehydrogenation experiments and on the nature of the side chain, a regular tetracyclic triterpenoid carbon skeleton has been assigned to them, and structures Ia and Ib have been proposed for elatericin B and elaterin[5] respectively. We now wish to report our experimental results leading to the modification of their structures to IIa and IIb. By previous

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1 This investigation was supported by a research grant CY-2810 from the National Cancer Institute of the National Institutes of Health, U.S. Public Health Service.

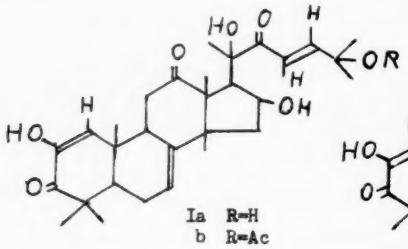
2 This communication is part XVIII in the series : The Constituents of Ecballium Elaterium L., part XVII : D. Lavie, Y. Shvo and O.R. Gottlieb, Tetrahedron Letters No. 22, 23 (1960).

3a Research fellow at Sloan-Kettering Institute for Cancer Research, New York, 1960-1961; b research fellow of the Conselho Nacional de Pesquisas on leave of absence from the Instituto de Química Agrícola, Ministério da Agricultura, Rio de Janeiro, Brazil.

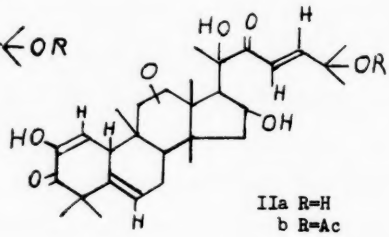
4 S. Gitter, R. Gallily, B. Shohat and D. Lavie, Cancer Res. 21, 516 (1961).

5 D. Lavie and Y. Shvo, Chem. & Ind. 403 (1960) and ref. 2.

correlation,[6] the structures of elatericin A and cucurbitacin B can be derived.



Ia R=H
b R=Ac



IIa R=H
b R=Ac

Noller, Shoolery et al.[7] have reported nuclear magnetic resonance (NMR) data for diosphenol systems. When a proton was present at the γ carbon atom of such $\alpha\beta$-unsaturated α-hydroxyketone systems, a spin-spin doublet centred at $\delta = 5.68$ was observed. Alternatively, if a hydrogen was not present on the γ carbon atom, a singlet at $\delta = 6.37$ was recorded. In both cases this signal is attributed to the vinylic hydrogen of the diosphenol system. Since a doublet, centred at $\delta = 5.97$ was found for a compound formed by the air oxidation of dihydro-cucurbitacin B, a hydrogen atom must be present at the γ carbon atom of the newly formed diosphenol system.[7] We were able to confirm these observations using dihydroelaterin (dihydro IIb) which showed a doublet centred at $\delta = 5.97$[10] ($J = 2$ cps), while a model compound, 4,4-dimethyl cholestane-2,3-dione[8] exhibited a single sharp peak at $\delta = 6.35$. Dihydroelatericin A,[6] in which the ring A double bond is

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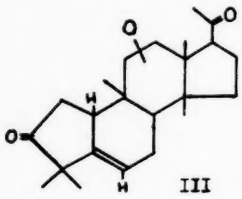
[6] D. Lavie, Y. Shvo and D. Willner; P.R. Enslin, J.M. Hugo and K.B. Norton, Chem. & Ind. 951, (1959).

[7] C.R. Noller, A. Melera and M. Gut; J.N. Shoolery and L.F. Johnson, Tetrahedron Letters No. 15, 15 (1960).

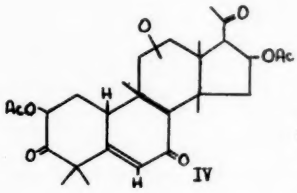
[8] A.P. Sigg and Ch. Tamm, Helv.Chim.Acta 43, 1402 (1960) compound XXVIII ; G.R. Chaudhry, T.G. Halsall and E.R.H. Jones, J.Chem.Soc. 2725 (1961).

saturated, showed no signals in this region of the spectrum. Since it is impossible to accommodate a diosphenol system with a γ proton in ring A of I, the methyl groups cannot possess the usual tetracyclic triterpene pattern; either a C-4 or the C-10 methyl is missing. A revision of the proposed structure was therefore necessary.

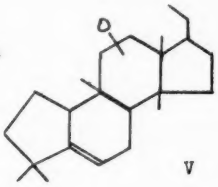
The NMR spectra of 16-desoxy-A(2)-nor-hexanor-elatericin A[5] (III) and cucurbitone D[9a] (IV), as well as other degradation products in which the side chain was removed, all showed five strong signals in the region assigned for methyl groups; an additional strong peak was recorded at δ = 2.08 and is related to a methyl ketone. In no case splittings of these signals could be observed, thus excluding the presence of a secondary methyl ($\rangle CHCH_3$). Consequently it must be concluded that five angular methyls are attached to the carbocyclic skeleton of the cucurbitacins.



III



IV



V

Three out of the five methyl groups should be placed at C-4, C-13 and C-14, since dehydrogenations of the various cucurbitacins[11] yielded

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9a P.R. Enslin, J.M. Hugo, K.B. Norton and D.E.A. Rivett, J.Chem.Soc. 4779 (1960); b A. Melera, M. Gut and C.R. Noller, Tetrahedron Letters No. 14, 13 (1960).

10 Positions of single peaks and centres of multiplets are expressed in dimentionless "chemical shift" units : $\delta = \frac{\Delta\,(TMS)}{R.f} \times 10^6$ p.p.m.
The term Δ (TMS) is the distance in cps from the tetramethyl silane signal (internal standard) which was taken as zero reference line. The spectra were calibrated by the "side band" technique using an audiofrequency oscillator.

11 P.R. Enslin and D.E.A. Rivett, J.Chem.Soc. 3682 (1956); D. Lavie and Y. Shvo, J.Amer.Chem.Soc. 82, 966 (1960).

repeatedly 1,2,8-trimethyl phenanthrene. According to extensive previous work, the isolation of this degradation product reveals the presence of methyl groups at C-13, C-14 and C-4 in the original tetracyclic triterpene molecule. In order to satisfy the NMR requirement for the absence of a $>CHCH_3$ grouping, an additional methyl must be secured at C-4, forming a gem-dimethyl structure. The presence of such a structure in the molecule was further substantiated by the presence of three absorption bands in the infra-red spectrum of V : 1384, 1377 and 1367 cm^{-1}. The splitting of the hydrogen deformation bands at 1384 and 1377 are in good agreement with the previously recorded observations for the presence of a gem-dimethyl group.[12] Compound V was used for this measurement to eliminate the absorption of the methyl ketone in this region of the spectrum; it was prepared by desulphurization of the bis-thioketal of III.

Having ascertained the presence of two methyls in ring A and two between rings C and D, three tertiary positions are left to be considered for the location of the remaining methyl group excluded from C-10, namely positions 5,8 and 9.

We have repeated the selenium dehydrogenation of elatericin A and isolated, beside the previously reported 1,2,8-trimethyl phenanthrene,[11] a naphthalene derivative possessing an ultra-violet spectrum superimposable on that of 1,2,5-trimethyl naphthalene. The isolation of such a degradation product is indicative of the presence of a methyl group at the B/C rings juncture.[13]

We have previously described[5] the formation of a ring B homoannular diene, λ_{max} 275 mμ (ϵ = 7800), during the treatment of the bisketal of III

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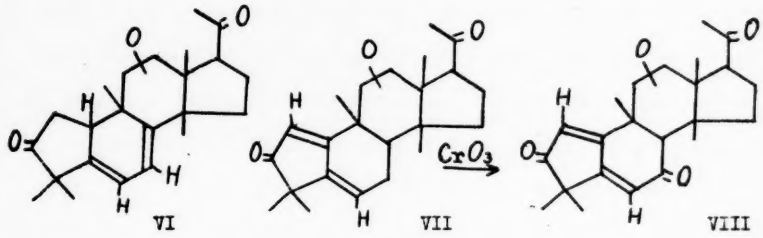
[12] L.J. Bellamy, The Infra-red Spectra of Complex Molecules p.24 Methuen, London (1959).

[13] D.H.R. Barton et al., J.Chem.Soc. 876 (1955); F.G. Fischer and N. Seiler, Leibigs Ann. 626, 185 (1959).

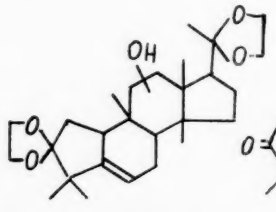


VI VII VIII

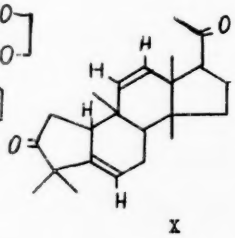
with N-bromosuccinimide. The nature of the diene, having two trisubstituted double bonds was indicated by its infra-red spectrum, a strong new band was recorded at 820 cm^{-1}. This band has been related to the bending vibrations of the two C-H groups at C-6 and C-7. Considering the presence of the methyl groups at C-13 and 14, any other possible homoannular diene in rings B or C should have one cis-disubstituted double bond which should display a band in the 700 cm^{-1} region. However, no absorption was recorded in that region. The NMR spectrum of this diene indicated two doublets centred at δ = 5.42 and 5.62 (J = 4 cps). Only one of these doublets was further split by about 2 cps and, consequently only one allylic proton flanks this diene system. Since it has already been shown that a proton exists at the C-10 position, it follows that C-9 (and C-13) must be occupied by a methyl, and only structure VI (with subsequent hydrolysis of the ketals) can represent this diene. A second product of this reaction, which was obtained in minor quantities, indicated which of the two double bonds of the diene VI corresponds to the original trisubstituted ethylenic linkage in the cucurbitacins. Structure VII, which corresponds to allylic bromination of the C-10 position followed by dehydrobromination, was assigned to this product. The infra-red spectrum of the carbonyl region showed one strong band at 1707 cm^{-1} related to the three carbonyls present in the molecule. This lowering of the five membered ring ketone absorption band,

which is present in III (1742 cm $^{-1}$), clearly indicates that it is the five membered ring carbonyl which underwent conjugation. Its ultra-violet spectrum λ_{max} 289 mμ (ϵ = 9000) is consistent with the calculated value. This structure was further supported by oxidation of VII with chromium trioxide in acetic acid yielding a yellow crystalline substance, $C_{23}H_{28}O_4$, m.p. 176-8°, λ_{max} 282 mμ (ϵ = 18,700); ν_{max} 1717, 1709, 1666 and 1569 cm^{-1} to which formula VIII is ascribed. Its NMR spectrum showed two doublets at low field centred at δ = 6.08 and 6.21 (J = 1 cps) and is related to the two vinylic protons which couple their spins, presumably through the conjugated system. Such an allylic oxidation of the nuclear trisubstituted double bond has been encountered in this series of compounds.[9a] The conjugated dienone system in VII clearly locates the inert double bond of the cucurbitacins in ring B between carbon atoms 5 and 6, and also requires a free access for conjugation between rings A and B through carbon atom 10.

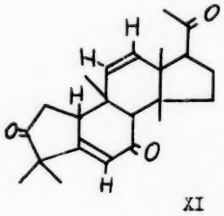
In order to adduce complementary evidence for the assignment of a methyl group at C-9, a sequence previously described[5] was reinvestigated. The bisketal of III was reduced with lithium aluminium hydride yielding the hydroxy bisketal (IX), the hydroxyl group being at 11 or 12. Dehydration of IX with phosphorous oxychloride in pyridine at room temperature (with



IX



X



XI

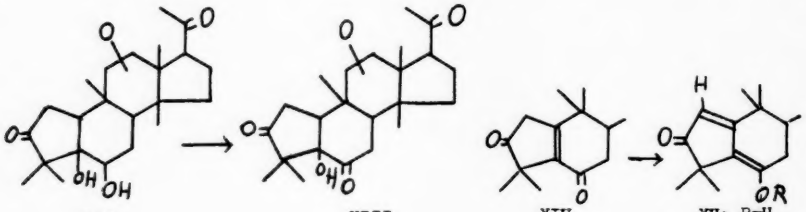
subsequent hydrolysis of the ketals), resulted in the formation of a double bond (Δ^{11}) as shown in formula X. The infra-red spectrum of X showed bands

at 1735 and 1708 cm^{-1} related to the five-membered carbonyl and the methyl ketone respectively. In addition a new and strong band appeared at 740 cm^{-1} related to the bending vibration of the newly formed cis double bond. The NMR spectral evidences for X were instructive, since they offered means to study the nature of the two carbons adjacent to the newly formed ethylenic linkage. A symmetrical pattern of lines was observed, forming two doublets centred at δ = 5.28 and 6.00 with equivalent splitting (J = 10 cps). Such a symmetrical pattern of lines was expected for a system of 2 vinylic protons as in 11 and 12 having no vicinal protons for further splitting of the signals by spin-spin coupling. A wide non resolved band was also observed in the vinylic hydrogens region at δ = 5.63. This signal is related to the C-6 proton, and it is unresolved due to spin-spin interaction with the two protons at C-7, and with the allylic proton at C-10 (it is noteworthy that the cucurbitacins, as well as compound III, all exhibit identical unresolved band in the vinylic hydrogen region). In order to indicate the relationship of this unresolved band to the vinylic hydrogen at C-6, the NMR spectrum of the allylic oxidation product of X was analysed. This product (XI), has the following characteristics: ν_{max}^{KBr} 1750 (five-membered ring ketone), 1709 (C-20 carbonyl), 1661 (conjugated carbonyl), 1653 (conjugated double bond), 745 (cis substituted double bond) cm^{-1}; λ_{max} 242 mμ (ϵ = 8720); its NMR spectrum showed again the four line system of the two Δ^{11} protons, while the original unresolved peak appears now as a neat doublet,[14] δ = 5.96 (J = 2 cps). The introduction of the oxygen at C-7 eliminated the spin-spin coupling of the C-7 protons with the vinylic proton, which now couples its spin only with a single allylic hydrogen present at C-10, leading therefore to the expected doublet. The downfield shift of the original signal is

[14] L.M. Jackman, Applications of Nuclear Magnetic Resonance Spectroscopy in Organic Chemistry p. 85, cf. ref. 9b Pergamon Press, London, New York (1959).

pertinent to the deshielding ability of the carbonyl group. These evidences show once more that the methyl group, previously allocated at C-10 is in fact attached to C-9, and that the nuclear double bond is situated between carbon atoms 5 and 6.

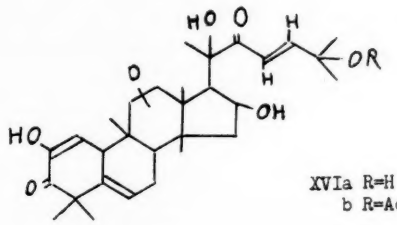
In light of the new observations, a sequence of experiments described earlier[5] and involving the hydroxylation of the nuclear double bond in ring B with OsO_4, was reinvestigated. This hydroxylation reaction led to the secondary-tertiary glycol (XII), which was subsequently oxidized with



chromium trioxide in acetone to the tetraketone (XIII). When heated to reflux in benzene with p-toluene sulphonic acid, XIII underwent dehydration. However, instead of an expected neutral product (which can now be formulated as XIV), a crystalline substance with acidic properties was isolated from the reaction mixture: m.p. 200° (decomp.) ν_{max} 3500,1750 (weak), 1700, 1660, 1605 and 1540 cm^{-1}; λ_{max} 335 and 405 mμ (ϵ = 10,300 and 3,100), $\lambda_{max}^{1\%KOH}$ 405 mμ (ϵ = 21,700). The system proposed in the previous formulation,[5] which would be consistent with the above experimental data, involved rings B and C. The band observed at 1750 cm^{-1} was thought to be indicative of a non-conjugated five-membered ring ketone in the molecule. However, careful comparisons of the absorption intensities of the different bands indicated that this band is in fact of a much weaker intensity than would be expected for a carbonyl group. This was also true for the intensity of the band at

1660 cm^{-1} which is now related to the $\alpha\beta$-unsaturated carbonyl at C-6 (XIV). The spectrum of the reaction product was measured in chloroform, and apparently, the solution must contain a mixture of the two tautomeric forms XIV and XVa. Indeed when this product was acetylated, XVb was obtained in pure form, its infra-red spectrum showed the following major bands: 1765 (enol acetate), 1707 (strong), 1557 cm^{-1}. No absorption band for a saturated five membered ring ketone was observed, as well as no indications were present for an $\alpha\beta$-unsaturated carbonyl in a six-membered ring. The NMR spectrum of XVb showed a single line at $\delta = 5.55$ for the vinylic proton situated at C-1.

In view of these observations we propose to revise the structures of elatericin B and elaterin to IIa and IIb, the hindered carbonyl being situated at either C-11 or C-12. Consequently elatericin A and cucurbitacin B, which have been previously related to these substances[6] have structures XVIa and XVIb.



XVIa R=H
b R=Ac

The relative configurations of several asymmetric centres in the cucurbitacins have been established. These results are not included in this communication, and the formulae as written here are without stereochemical implications.

Tetrahedron Letters No. 18, pp. 624-627, 1961. Pergamon Press Ltd. Printed in Great Britain.

1961

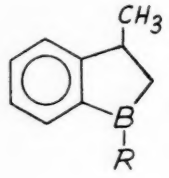
ÜBER DIE VERBINDUNGEN AUS BORA-INDANEN UND ALKALIMETALLEN

W. Grimme, K. Reinert und R. Köster*

Max-Planck-Institut für Kohlenforschung, Mülheim-Ruhr

(Received 21 September 1961)

BORA-Indane[1] bilden mit Alkalimetallen (Natrium, Kalium) kristallisierte, in aromatischen Kohlenwasserstoffen mehr oder weniger gut lösliche, farblose Verbindungen, die aus 1 Mol Bora-indan und 1 g-atom Alkalimetall zusammengesetzt sind. Sie gleichen damit den Verbindungen aus Natrium und Triphenylboran[2] bzw. Tribenzylboran,[2] die nach unseren Ergebnissen ebenfalls vollkommen farblose Stoffe sind.



+ M ⟶ 1:1-"Addukt"

M = Na; K

z.B. R = CH_2-$CH(CH_3)C_6H_5$ und M = Na: unscharfer Schmelzpunkt von 124-135°C.

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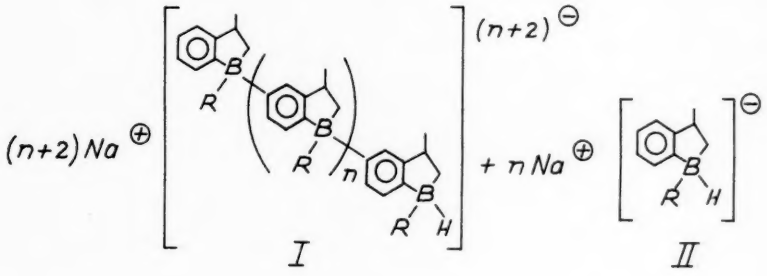
* Correspondence should be addressed to this author.

1 R. Köster und K. Reinert, Angew.Chem. 71, 521 (1959).

2 E. Krause, Ber.Dtsch.Chem.Ges. 57, 216 (1924); weitere Veröffentlichungen über die Triarylbor-natrium-verbindungen vgl. G.E. Coates, Organometallic Compounds pp. 112-114. Methuen, London; John Wiley, New York (1960).

Erwärmt man eine benzolische Lösung von B-Alkylbora-indanen oder B-Aralkylbora-indanen in Gegenwart von metallischem Natrium (z.B. als Draht oder auch als Amalgam), so bilden sich zunächst gefärbte Lösungen, deren Elektronenresonanz auf freie Radikale (als Zwischenverbindungen) hinweist. Nach und nach scheiden sich farblose, diamagnetische Verbindungen ab. Das Molgewicht dieser Stoffe (Gefrierpunktserniedrigung in Benzol) entspricht etwa dem 5-6 fachen Wert der einfachen Formel des 1:1-"Addukts".

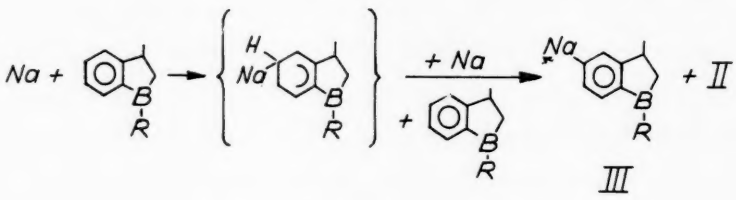
Wir konnten feststellen, dass es sich bei diesen Verbindungen um K o m p l e x s a l z e mit 4-bindigen Boratomen handelt, denen folgendes Strukturprinzip zungrunde liegen muss.



I II

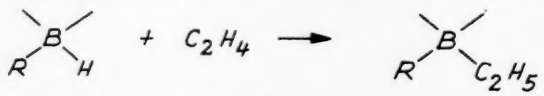
Die bei der Bildung der Komplexsalze zu beobachtenden Farbveränderungen weisen auf verschiedene Reaktionsstufen hin. Wir vermuten, dass die nucleophile Substitution durch Alkalimetall am Phenylkern der erste Schritt ist. Eine unmittelbare Wechselwirkung zwischen Natriummetall und den Boratomen der Arylborane, wie sie bisher immer angenommen wurde, halten wir für unwahrscheinlich.

Die Verbindung III bildet dann mit ihresgleichen die hochmolekularen Salze mit 4-bindigem Bor (Typ I).



Die vorgeschlagenen Strukturformeln I und II werden durch folgende experimentelle Ergebnisse gestützt. In den Salzen lassen sich eindeutig B-H-Bindungen nachweisen. Wie bei den Komplexsalzen aus Natriumhydrid und Bortrialkylen[3] bzw. aus Natriumhydrid und Bora-indanen[4] beobachtet man eine breite Absorptionsbande für die B-H-Bindung zwischen 1850 und 2200 cm^{-1} mit Maxima bei 1950 und 1970 cm^{-1}.[5] Ausserdem sprechen folgende Reaktionen für das Vorhandensein der B-H-Gruppen:

(a) Bei der Einwirkung von Olefinen (z.B. Äthylen unter Druck bei 150°C) bilden sich die entsprechenden B-Alkylverbindungen, wobei sämtliche B-H-Bindungen verschwinden. Bei der Alkoholyse wird anschliessend kein Wasserstoff mehr entwickelt.



(b) Die Deuterolyse der Verbindungen liefert in der berechneten Menge ausschliesslich Wasserstoffdeuterid.

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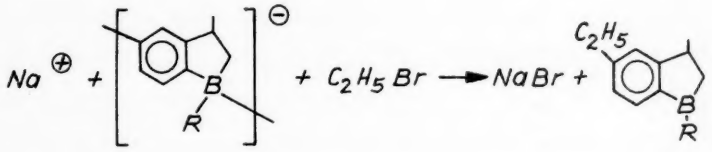
[3] vgl. J.B. Honeycutt, Jr. und J.M. Riddle, J.Amer.Chem.Soc. 83, 369 (1961); sehr starke, breite Bande bei 1850 cm^{-1} beim Natriumtriäthylborhydrid.

P. Binger und R. Köster, unveröffertlicht; Natriumtripropylborhydrid (gelöst in Hexan) zeigt eine breite Bande zwischen 1750-1950 cm^{-1} mit Maximum bei 1830 cm^{-1}.

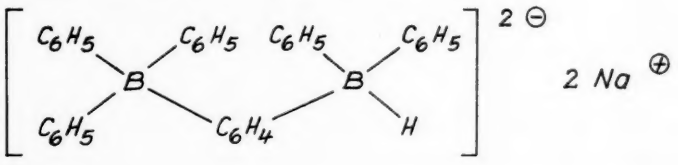
[4] Die Komplexverbindung aus NaH und B-(2-Phenylpropyl)-3-methylboraindan (Schmp. = 186°C) zeigt in benzolischer Lösung eine breite IR-Bande zwischen 1850 und 2200 cm^{-1} mit Maxima bei 1950 und 1970 cm^{-1}.

[5] Die Verbindungen aus Natrium und Triphenylboran bzw. Natrium und Tribenzylboran haben, gelöst in Tetrahydrofuran, ebenfalls eine breite B-H-Bande zwischen 1900 und 2000 cm^{-1} mit Maximum bei 1970 cm^{-1}.

Bei der Umsetzung der Bora-indan-natrium-verbindungen mit Äthylbromid in benzolischer Lösung bei Raumtemperatur wird Natriumbromid abgeschieden. Unter den gebildeten nicht salzartigen Verbindungen lässt sich durch IR-Spektroskopie ein Bora-indan nachweisen, das einen 1,2,4-trisubstituierten Phenylkern enthält (IR-Bande bei 821 cm^{-1}).



Da sich die Bora-indan-alkalimetall-"addukte" unter den gleichen Bedingungen bilden wie die "Additionsprodukte" aus Alkalimetallen und Triarylboranen[1] und ausserdem z.B. dem Triphenylbor-natrium in ihren Eigenschaften[5] und Reaktionen sehr ähnlich sind, vermuten wir, dass die Struktur dieser Verbindungen derjenigen der Bora-indan-alkalimetall-verbindungen analog ist. Das Bortriphenyl-natrium sollte demnach als Komplexsalz mit 4-bindigem Bor u.a. folgendes Bauelement enthalten.



Tetrahedron Letters No. 18, pp. 628-631, 1961. Pergamon Press Ltd. Printed in Great Britain.

ORIENTATION IN ISOFLAVONES

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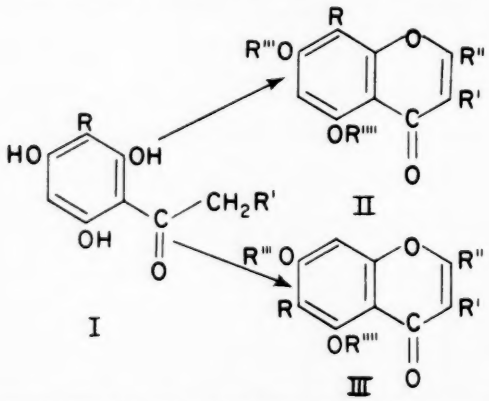
Chemistry Department, Muslim University, Aligarh/India

(Received 22 September 1961)

IN our earlier communication[1] it has been observed that the deoxybenzoin (I; R = Me, R' = C_6H_5) on submitting to ethoxalylation process gives a mixture of 5:7-dihydroxy-8-methyl- and 5:7-dihydroxy-6-methyl isoflavones (II and III; R = Me, R' = C_6H_5, R'' = R''' = R'''' = H) resulting from the cyclization involving 2- and 6-hydroxyl groups respectively. An explanation for the dual course of cyclization has also been advanced.



After completing this study we came across the work of Mehta and Seshadri[2] where they have reported that the deoxybenzoin of a similar type

[1] M.O. Farooq, W. Rahman and Kh. Takrimullah Nasim, J.Org.Chem. In press (1961).

[2] A.C. Mehta and T.R. Seshadri, J.Chem.Soc. 3823 (1954).

(I; R = Me, R' = p-MeO.C_6H_4) on ethoxalylation yields finally only one isomer, 5:7-dihydroxy-4'-methoxy-6-methyl isoflavone (III; R = Me, R' = p-MeO.C_6H_4, R'' = R''' = R'''' = H). According to our explanation[1] as to the course of cyclization of the deoxybenzoins of the above type with ethoxalyl chloride, the formation of one isomer and that too of 5:6:7-orientation appeared to be inconceivable. The reinvestigation of ethoxalyation of 2:4:6-trihydroxy-3-methyl-4'-methoxydeoxybenzoin (I; R = Me, R' = p-MeO.C_6H_4) appeared of interest and therefore the present work was undertaken.

The deoxybenzoin (I; R = Me, R' = p-MeO.C_6H_4) on ethoxalylation gave a product m.p. 176-78°. This product was assigned the structure of ethyl 5:7-dihydroxy-4'-methoxy-6-methyl isoflavone-2-carboxylate (III; R = Me, R' = p-MeO.C_6H_4, R'' = CO_2Et, R''' = R'''' = H) by Mehta and Seshadri[2]. The carbethoxy isoflavone (III; R = Me, R' = p-MeO.C_6H_4, R'' = CO_2Et, R''' = R'''' = H) on hydrolysis yielded the corresponding carboxyisoflavone (III; R = Me, R' = p-MeO.C_6H_4, R'' = CO_2H, R''' = R'''' = H). The melting point of the acid is not, however, reported. The crude carboxyisoflavone on decarboxylation at 275° gave an isoflavone m.p. 210-212°. It was characterized by them as 5:7-dihydroxy-4'-methoxy-6-methyl isoflavone (III; R = Me, R' = p-MeO.C_6H_4, R'' = R''' = R'''' = H) by partial methylation to 5-hydroxy-7:4'-dimethoxy-6-methyl isoflavone (III; R = R''' = Me, R' = p-MeO.C_6H_4, R'' = R'''' = H). The latter showed no depression in melting point on admixture with the nuclear methylation product of genistein.[3]

The product m.p. 176-178° (erroneously assigned the structure of ethyl 5:7-dihydroxy-4'-methoxy-6-methyl isoflavone-2-carboxylate by Mehta and

[3] W. Baker and R. Robinson, J.Chem.Soc. 2713 (1926).

Seshadri[2]) was found by the present authors, to be a mixture of two isomers very difficult to separate. It was, however, resolved by a careful fractional crystallization from benzene-methanol into two distinct products melting at 199-201° and 201-203°. The mixed melting point of the two isomers was found to be 176-178° as reported by the previous workers[2] for one component.

The carbethoxyisoflavone melting at 199-201° on usual hydrolysis and decarboxylation gave the corresponding carboxy- and then hydroxy-isoflavone m.p.'s 280-281° and 235-236° respectively. The latter was characterized as 5:7-dihydroxy-4'-methoxy-8-methyl isoflavone (II; R = Me, R' = p-MeO.C_6H_4, R'' = R''' = R'''' = H) by its complete methylation to 5:7:4'-trimethoxy-8-methylisoflavone (II; R = R''' = R'''' = Me, R' = p-MeO.C_6H_4, R'' = H) m.p.[4] and mixed m.p. 180°.

The carbethoxyisoflavone m.p. 201-203° (III; R = Me, R' = p-MeO.C_6H_4, R'' = CO_2Et, R''' = R'''' = H) on similar treatment as above yielded the corresponding carboxyisoflavone m.p. 288-91° (III; R = Me, R' = p-MeO.C_6H_4, R'' = CO_2H, R''' = R'''' = H) and then an isoflavone. It was characterized as 5:7-dihydroxy-4'-methoxy-6-methyl isoflavone m.p. 260-263° (III; R = Me, R' = p-MeO.C_6H_4, R'' = R''' = R'''' = H) by the preparation of its complete methyl ether m.p. 169°. It showed no depression in melting point on admixture with an authentic sample[5,6] of 5:7:4'-trimethoxy-6-methyl isoflavone (III; R = R''' = R'''' = Me, R' = p-MeO.C_6H_4, R'' = H).

The ethoxalylation of 2:4:6-trihydroxy-3-methyl-4'-methoxy deoxybenzoin (I; R = Me, R' = p-MeO.C_6H_4) resulting in the formation of isomeric isoflavones of 5:6:7- and 5:7:8-orientations lends support to our previous

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[4] W.B. Whalley, J.Amer.Chem.Soc. 75, 1059 (1953).

[5] W.B. Whalley, J.Chem.Soc. 3366 (1953).

[6] W.B. Whalley, Chem.&Ind. 277 (1953).

findings[1] and is not in agreement with the findings of Mehta and Seshadri [2]. Further confirmation to our findings has been furnished by the investigation of ethoxalylation of 2:4:6-trihydroxy-3-methyl-2'-methoxy deoxybenzoin (I; R = Me, R' = o-MeO.C_6H_4) where again in isomeric mixture of 5:6:7- and 5:7:8-isoflavones has been obtained.

The full details of this work will appear elsewhere.

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THE REACTIVITY AND ELECTRONIC SPECTRA OF PSEUDOAROMATIC SULPHUR COMPOUNDS

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(Received 3 October 1961)

PSEUDOAROMATIC sulphur compounds which we have studied by means of the simple MO-LCAO method can be divided into four groups according to the parent substances from which they can be formally derived by the substitution of the -CH=CH- group by a sulphur atom. The compounds under consideration are analogues of tropylium (I) [thiapyrylium (II), 1,2-dithiylium (III), 1,3-dithiylium (IV)], benzotropylium (V) [1-thianaphtylium (VI), 2-thianaphtylium (VII), benzo-1,3-dithiylium (VIII)], azulene (IX) [thialene (X), isothialene (XI)], tropone (XII) [α- and γ-thiapyrones (XIII,XIV), derivatives of 1,2- and 1,3-dithiylium (XV,XVI; Y=O,S)] and tropolone (XVII) [3-hydroxythiapyrones (XVIII; Y=O,S)] (Fig. 1). Except the compounds nos. XIII-XVI, already known for a longer time, all these substances have been synthesized recently.[1-11] The compounds II and VIII were studied

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1 R. Pettit, Tetrahedron Letters No. 23, 11 (1960).
2 A. Lüttringhaus and N. Engelhard, Angew.Chem. 73, 218 (1961).
3 E. Klingsberg, Chem. & Ind. 1568 (1960).
4 D. Leaver and W.A.H. Robertson, Proc.Chem.Soc. 252 (1960).
5 D. Leaver, private communication concerning the compound IV.
6 A. Lüttringhaus and N. Engelhard, Chem.Ber. 93, 1525 (1960).

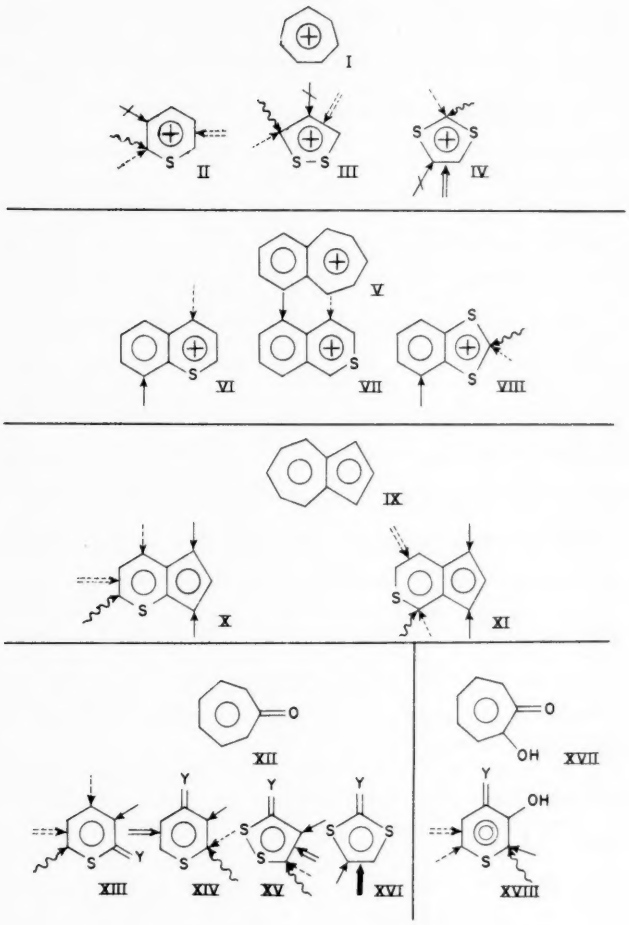

FIG. 1. Survey of the compounds studied together with the data on reactivity centres; for symbols cf.text. (Data concerning the compounds X and XI given in paper 8 are from the perturbation calculations; the values presented here result from the secular equations; XVI: model without considering d-orbital.)

theoretically earlier.[12,13] The results of the reactivity calculations based on the Longuet-Higgins model of the hybrid pd^2 sulphur orbitals are summarized in Fig. 1. ($\beta_{CS} = 0.6\,\beta$; exocyclic atoms: $\alpha_O = \alpha_C + 2\beta$, $\alpha_S = \alpha_C + 0.5\beta$, $\beta_{CO} = \sqrt{2}\beta, \beta_{CS} = 0.9\beta$). The predictions are based on the π-electron densities (polar substitutions), free valences (radical substitutions) and bond orders (addition reactions). The information for VI and VII is based on the perturbation calculations; all other data result from the solutions of the secular equations. The theoretical centres of electrophilic, nucleophilic and radical reactivities are marked with arrows (↓, ⇣, ⇵, resp.); a double arrow indicates a bond of maximum order (bond order lower than 0.8 ⇣, 0.8-0.9 ⇊, higher than 0.9 ⇓). Should a reaction of certain type be improbable the respective arrow is crossed out. The theoretical data are in agreement with all experimental data hitherto published.[8,9,14-16] The compounds have been studied by means of a model involving the participation of the sulphur d-orbitals; besides this, many compounds have been investigated by means of a model without considering the d-orbitals ($\alpha_S = \alpha_C + \beta$;

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7 L. Soder and R. Wizinger, Helv.Chim.Acta 42, 1779 (1959).

8 R. Mayer, J. Franke, V. Horák, I. Hanker and R. Zahradník, Tetrahedron Letters No. 9, 289 (1961).

9 A.G. Anderson, Jr., W.F. Harrison, R.G. Anderson and A.G. Osborne, J.Amer.Chem.Soc. 81, 1255 (1959).

10 A.G. Anderson, Jr., and W.F. Harrison, Tetrahedron Letters No. 2, 11 (1960).

11 V. Horák and N. Kucharczyk, Chem. & Ind. 694 (1960).

12 J. Koutecký Coll.Czech.Chem.Comm. 24, 1608 (1959).

13 J. Koutecký, J. Paldus and R. Zahradník, Coll.Czech.Chem.Comm. 25, 617 (1960).

14 R. Zahradník, C. Párkányi and J. Koutecký, Coll.Czech.Chem.Comm. In press.

15 C. Párkányi and R. Zahradník, Coll.Czech.Chem.Comm. In press.

16 F. Challenger, E.A. Mason, E.C. Holdsworth and R. Emmott, J.Chem.Soc. 292 (1953).

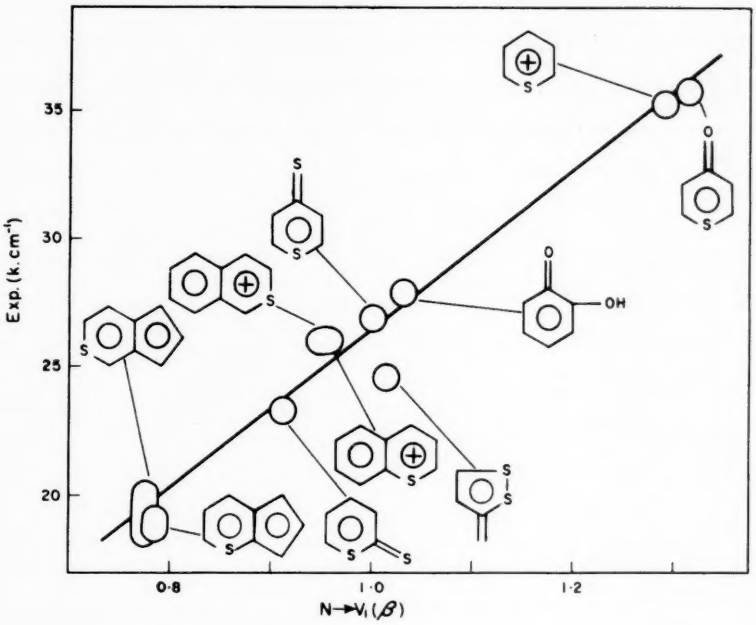

FIG. 2. Energy of the first long-wave absorption maximum of the electronic spectrum plotted against the theoretical value of the $N \rightarrow V_1$ transition.

$\beta_{CS} = 0.6\,\beta$). Contradictory predictions of the position of the maximum reactivity (e.g. for 2-naphtylium) could contribute to the solution of the problem of a suitable model for the sulphur atom orbitals.

Moreover, we have found rather a close linear correlation between the theoretical $N \rightarrow V_1$ energies and the energies of the first intense absorption maximum in the electronic spectrum (Fig. 2). The slope of this dependence is 30.8 kcm^{-1}/β (βmeans the energy unit of the simple MO method) and is evidently higher than that one for aromatic hydrocarbons where it amounts to 19.5 kcm^{-1}/β.

A more detailed discussion of the reactivity based on static and dynamic indices, the comparison of the models for the sulphur atomic orbitals and the prediction of existence and properties of further pseudoaromatic sulphur compounds will be published in Coll.Czech.Chem.Comm.

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ON ORTHO-TERTIARYBUTYLBENZENES

1,2,4,5-TETRA-TERTIARYBUTYLBENZENE

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THE problem of the possible existence of a benzene with two t-butyl groups in the o-position has long been of interest. After studying reactions with homomorphs of di-o-t-butylbenzene Brown et al.[1] came to the conclusion that the synthesis of di-o-t-butylbenzene will probably require reactors of unusually high driving force and the avoidance of conditions conducive to molecular rearrangement and isomerization. The unsuccessful attempts[2] recently made in this field again show the difficulty of the problem. Some time ago we accomplished the synthesis of 1,2,4-tri-t-butylbenzene by treating the complex $Co_2(CO)_4(C_6H_{10})_3$, made from t-butylacetylene (C_6H_{10}) and $Co_2(CO)_8$, with bromine.[3] From spectroscopic data Dale[4] pointed out that the benzene ring in 1,2,4-tri-t-butylbenzene is distorted, so compensating the steric requirements for the bulky t-butyl groups. Starting from o-phenylene-di-isobutyric acid[5] Barclay et al.[6] prepared β,β'-di-hydroxy-o-di-t-butyl-

[1] H.C. Brown, D. Gintis and L. Domash, J.Amer.Chem.Soc. 78, 5387 (1956).

[2] For literature see ref. 3.

[3] U. Krüerke, C. Hoogzand and W. Hübel, Chem.Ber. In press.

[4] J. Dale, Chem.Ber. In press (1961).

[5] H.A. Bruson, F.W. Grant and E. Bobko, J.Amer.Chem.Soc. 80, 3633 (1958).

[6] L.R.C. Barclay, N.H. Hall and J.W. Maclean, Tetrahedron Letters No. 7, 243 (1961).

benzene which has a similar U.V. spectrum to 1,2,4-tri-t-butylbenzene. However they concluded that there should be no serious strain or distortion of the benzene ring. Dale's conclusion raised the question whether one could introduce more than three t-butyl groups in a benzene ring. For, if the steric requirements of the t-butyl groups really force the ring out of a planar configuration, further substitution of t-butyl groups might effect an additional distortion of the ring and so make more space for the bulky substituents.

We now wish to report two syntheses of 1,2,4,5-tetra-t-butylbenzene, the one achieved by means of a cobaltcarbonyl-complex, the other by a purely organic route.

The complex $Co_2(CO)_6C_{10}H_{18}$ was prepared by the known method[7] from $Co_2(CO)_8$ and di-t-butylacetylene ($C_{10}H_{18}$)[8] in ligroin at room temperature: yield 90%, dec. 115-120°. 21.2 g (0.05 mole) of this complex were refluxed in ligroin (b.p. 100-120°) with 24.6 g (0.3 mole) of t-butylacetylene[9] by adding the latter in six portions over a period of 60 hr. Repeated chromatography on neutral alumina gave with

(a) ligroin: 12.7 g of a mixture of unreacted $Co_2(CO)_6C_{10}H_{18}$, 1,2,4-tri-t-butylbenzene and 1,2,4,5-tetra-t-butylbenzene (I).

(b) ligroin/benzene: 3.2 g (13%) of violet $Co_2(CO)_4(C_6H_{10})_3$,[3] coming from $Co_2(CO)_6C_6H_{10}$ which is formed by alkyne exchange of $Co_2(CO)_6C_{10}H_{18}$.

(c) benzene and methylenechloride: 1.5 g of the unknown orange 2,3,5-tri-t-butylcyclopentadienone (II), m.p. 55-55.5° from methanol. (Found: C, 81.63; H, 11.45; O, 6.92. Calc. for $C_{17}H_{28}O$: C, 82.20; H, 11.36;

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[7] H. Greenfield, H.W. Sternberg, R.A. Friedel, J.H. Wotiz, R. Markby and I. Wender, J.Amer.Chem.Soc. 78, 120 (1956).

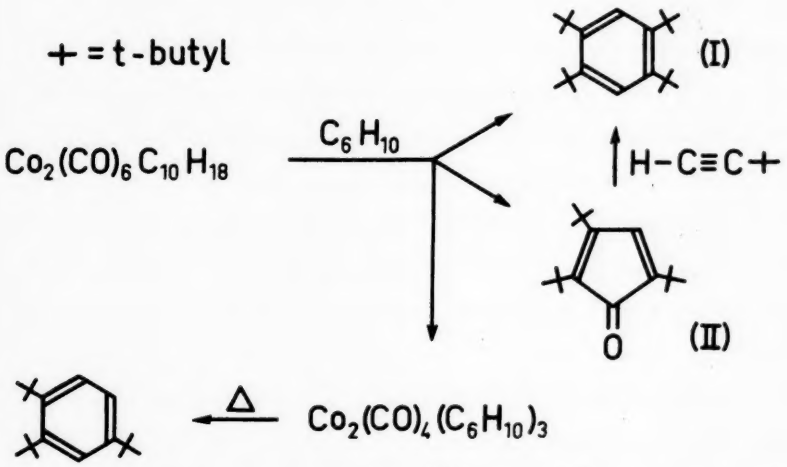
[8] G.F. Hennion and T.F. Banigan, Jr., J.Amer.Chem.Soc. 68, 1202 (1946).

[9] M.P. Ivitsky, Bull.Soc.Chim. [4] 35, 357 (1924); W.H. Puterbaugh and M.S. Newman, J.Amer.Chem.Soc. 81, 1611 (1959).

0, 6.44). The I.R. spectrum (KBr) shows a band at 5.83 μ, due to the ketonic group.

As fraction (a) was very difficult to separate the complex was decomposed in boiling ligroin (b.p. 80-100°C) in a stream of air. The residual oil (6.2 g) was recrystallized from methanol and yielded 1.6 g (11%) I; from the mother liquor a further 3.4 g of 1,2,4-tri-t-butylbenzene, m.p. 49-50°,[3] were isolated. I was recrystallized from benzene/methanol; m.p. 156.5 - 158.5°, corr. (Found: C, 87.48; H, 12.40; mol. wt. (Rast): 286 and 311. Calc. for $C_{22}H_{38}$: C, 87.34; H, 12.66; mol. wt.: 302.5).

Since 1,2,4-tri-t-butylbenzene can be prepared by thermal decomposition of $Co_2(CO)_4(C_6H_{10})_3$,[3] it is likely that I is also formed from the probably less stable $Co_2(CO)_4[(C_6H_{10})_2; C_{10}H_{18}]$ which decomposes during the reaction.



A similar reaction of $Co_2(CO)_6C_6H_{10}$[10] with $C_{10}H_{18}$[8] in boiling ligroin (b.p. 80-100°) gave only II in about 10% yield.

[10] M.R. Tirpak, C.A. Hollingworth and J.H. Wotiz, J. Org.Chem. 25, 687 (1960).

A second synthesis of I was found in the Diels-Alder reaction of II with t-butylacetylene. Heating both compounds in benzene in a sealed tube at 250° for 3 hr gave I in 70% yield. M.p. and I.R. spectrum were identical with those of I prepared by the first synthesis. Also the m.p. of the mixture showed no depression. This reactions proves the structure of II to be 2,3,5-tri-t-butylcyclopentadienone. It also represents the first preparation by a purely organic route of a benzene derivative with t-butyl groups in the ortho-position and is of general application. Thus when II and dicarbomethoxyacetylene were heated at 200° for a period of 10 min, 1,2,4-tri-t-butyl-5,6-dicarbomethoxybenzene was obtained in a 70% yield, m.p. 122-123° (from ethanol). (Found: C, 72.88; H, 9.12; O, 18.10. Calc. for $C_{22}H_{34}O_4$: C, 72.89; H, 9.45; O, 17.66.)

The structural proof for I is derived from NMR measurements. The spectrum at 60 Mc/s in CS_2 shows only two narrow bands of half-peak width about 1.5 cps without any fine structure: one band for aromatic protons at τ = 2.46 and the other for aliphatic protons at τ = 8.52,[10a] relative to tetra-methylsilane as internal standard τ = 10. Moreover the ratio of the peak areas (aromatic/aliphatic) is 2:34.5, which corresponds very well with the expected value 2 : 36. Also the high m.p. of I is in agreement with this structure; cf. the m.p. 119-119.4° of 1,2,4,5-tetra-isopropylbenzene[11].

The U.V. spectrum of I in n-hexane (Fig. 1) has the same pattern as that of 1,2,4-tri-t-butylbenzene:[4] λ_{max} in mμ (ϵ): 274 (359), 225 (sh., 12,500), 203.5 (56,500). 1,2,4,5-tetra-isopropylbenzene: λ_{max} in mμ (ϵ): 278 (662), 269 (587), 262 (sh., 328), 219 (infl., 13,500), 202 (65,000).

[10a] For 1,2,3,4 aud 1,2,3,5 substitution two (intensity 1:1) or three (intensity 1:1:2) peaks respectively have to be observed for the t-butyl-groups.

[11] V.N. Ipatieff, B.B. Corson and H. Pines, J.Amer.Chem.Soc. 58, 919 (1936).

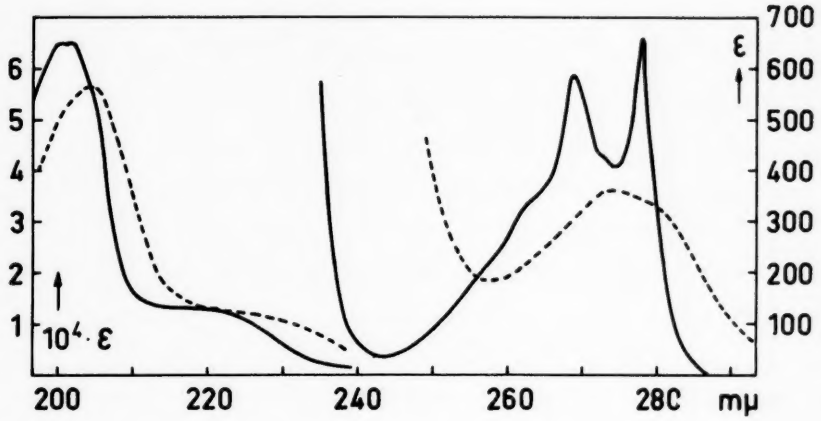


FIG. 1. U.V. spectrum in n-hexane.
---- 1,2,4,5-tetra-t-butylbenzene.
——1,2,4,5-tetra-iso-propylbenzene.

Comparing the spectrum of I with that of 1,2,4,5-tetra-isopropylbenzene,[12] which shows fine structure and higher values of ϵ in the 270μ region, we again conclude that the benzene ring is distorted.

Furthermore, the I.R. spectrum (Fig. 2) is in agreement with the assigned structure: the band at 11.21μ (KBr) must be attributed to the aromatic C-H out of plane vibration, which has practically the same position as in 1,2,4,5-tetra-isopropylbenzene (11.19μ). In $CHCl_3$ solution I has a weak band at 6.31μ, which may be attributed to a ring stretching frequency, normally only observable in the Raman spectrum of 1,2,4,5-tetra-akyl substituted benzenes.

The activity of this vibration indicates the loss of the centre of symmetry of I and would exclude a chair type form for the benzene ring. This leads to the conclusion that the benzene ring has been twisted into

[12] prepared following ref. 11.

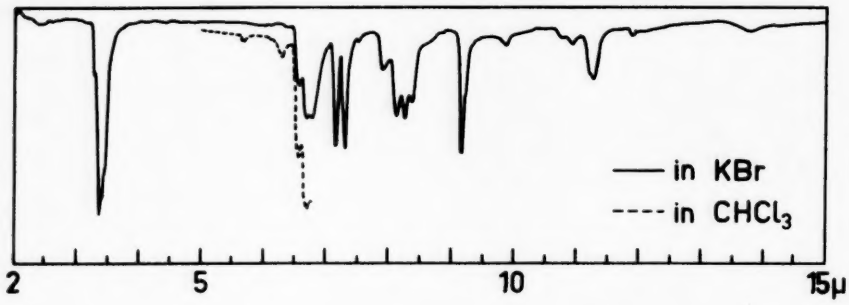


FIG. 2. I.R.-spectrum of 1,2,4,5-tetra-t-butylbenzene.

the "boat" form, comparable with one of the possible conformations for a cyclohexane ring. From a (too rigid) Stuart-Briegleb model it is indeed evident that a "boat" form is rather easy to realize and makes more space available for the bulky groups. Moreover the model suggests a structure in which the substituents on the ring carbon atoms 1,2,4 and 5 are alternating slightly upwards and downwards from the plane through these carbon atoms.

The heat of combustion of the solid I has been determined as 3295.9 ± 3 kcal/mole,[13] without taking into account the heat of sublimation. For a hypothetical undistorted tetra-t-butylbenzene a heat of combustion of 3264.9 ± 1.4 kcal/mole was calculated.[14] The difference between these values (31.0 ± 3.7 kcal/mole) still contains the difference in the heats of sublimation of I and 1,3,5-tri-t-butylbenzene as an unknown factor, being of the order of a few kcal/mole. Nevertheless it is evident that the resonance energy of I is considerably decreased.

This work was supported by Union Carbide Corporation New York, N.Y. We are indebted to Drs. R.H. Gillette and C.E. Sunderlin for their interest in this work. Acknowledgement is due to Messrs A. Gérondal and J.R. Senders

[13] For these measurements we are indebted to Dr. A. Reckziegel and Prof. E.O. Fischer, University of Munich.

[14] From the heats of combustion of 1,3,5-tri-t-butylbenzene,[3] t-butylbenzene: (2640.7 + 1413.3 - 789.1) ± 1.4 kcal/mole.

for technical assistance. We wish to express our thanks to Drs. J. Dale and J.F.M. Oth for their helpful discussions of the I.R.-, U.V.- and NMR spectra.

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THE SOLVOLYSIS OF BENZHYDRYL p-NITROBENZOATE-CARBONYL-^{18}O

A NEW METHOD FOR DETECTING ION PAIR RETURN

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(Received 22 September 1961)

RECENTLY[2] it was discovered that in the trans-5-methyl-2-cyclohexenyl p-nitrobenzoate system internal return results in equilibration of the carboxyl oxygen atoms at a rate greater than that of allylic rearrangement (racemization). This suggested that equilibration of carboxyl oxygen atoms might be a useful method for detecting ion pair return in systems which do not rearrange. This possibility had been investigated earlier with negative results - ether-^{18}O 2,4-dimethylhex-4-yl acid phthalate remains discretely labelled during solvolysis.[3]

We have now examined the solvolysis of carbonyl-^{18}O benzhydryl p-nitrobenzoate in 90% aqueous acetone and have found that the carboxyl oxygen atoms are indeed equilibrated during solvolysis. At 118.6° both solvolysis (followed titrimetrically) and oxygen equilibration are first-order.

The overall process can be summarized as follows.

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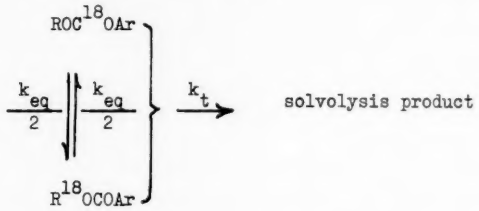
[1] National Science Foundation Fellow.

[2] H.L. Goering and J.T. Doi, J.Amer.Chem.Soc. 82, 5850 (1960).

[3] W.E. Doering, A. Streitwieser, Jr. and L. Friedman, Unpublished work cited by A. Streitwieser, Jr., Chem.Rev. 56, 663 (1956).



The first-order rate constant for equilibration of the carboxyl oxygen atoms in the unsolvolyzed ester [k_{eq}, equation (1)] is 18.7 x $10^{-3}hr^{-1}$. This reaction was followed by starting with ^{18}O-carbonyl-labelled ester and determining the ^{18}O distribution in the remaining ester at appropriate time intervals. The first-order rate constant for solvolysis, k_t, is 6.4 x 10^{-3} hr^{-1}[4] which is three times smaller than k_{eq}. From the high solvolytic reactivity it is clear that solvolysis involves alkyl-oxygen cleavage.[5]

$$ROC^{18}OAr \xrightarrow{k_{eq}} R^{18}OC^{18}OAr \qquad (1)$$

Since the first-order rates of solvolysis (followed to 75% completion) and oxygen equilibration (followed to 85% completion) are steady, except for the upward trend in k_t in experiments without added solutes,[4] it is apparent that equilibration must be largely intramolecular--equilibration at the observed rate by a dissociation-recombination mechanism (external

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[4] There is a rather large positive salt effect for solvolysis; k_t is increased about 20% by 0.042 M p-nitrobenzoic acid and 80% by 0.045 M lithium p-nitrobenzoate. Because of the salt effect k_t shows an upward trend in experiments without added solutes, e.g. the integrated constants drift from 5.7 x $10^{-3}hr^{-1}$ (12% reaction) to 6.6 x $10^{-3}hr^{-1}$ (75% reaction) and the initial rate constant, obtained by extrapolation, is about 5.5 x $10^{-3}hr^{-1}$. In experiments with added p-nitrobenzoic acid (0.015 to 0.043 M) good first-order behavior was observed.

[5] For additional evidence bearing on this point see M.S. Silver, J.Amer.Chem.Soc. 83, 404 (1961).

return) would require considerable drifts in both k_t (downward) and k_{eq} (upward).

The intramolecular nature of the oxygen equilibration process was established by an independent method. The rate at which the unsolvolyzed ester exchanges with p-nitrobenzoic acid under conditions of the solvolysis (and oxygen equilibration) was established using ^{14}C-labelled p-nitrobenzoic acid. This rate was found to be first-order in both ester and p-nitrobenzoic acid; the second-order constant is 2.0×10^{-2} l. $mole^{-1} hr^{-1}$. From this exchange constant, and the average p-nitrobenzoic acid concentration in the medium, the fraction of ester that will undergo exchange during any period can be computed. Under the conditions of the oxygen equilibration experiments the only p-nitrobenzoic acid present is that formed by solvolysis. From the rate of exchange between ester and p-nitrobenzoic acid it can be shown that under these conditions after 103 hr (86% equilibration of oxygen atoms) only 2.5% of the remaining ester will have undergone exchange. Clearly the oxygen equilibration process is essentially completely intramolecular in the sense that the alkyl group remains attached to the same carboxyl group.

Presumably the intromolecular oxygen-equilibration process which accompanies solvolysis involves ion pair return (probably internal return).[6,7] If the oxygen atoms in the intermediate ion pair (I) are equivalent, the rate constant for ionization (k_1) is ($k_{eq} + k_t$) and the rate constant for formation of that fraction of I which returns to substrate is k_{eq}. However,

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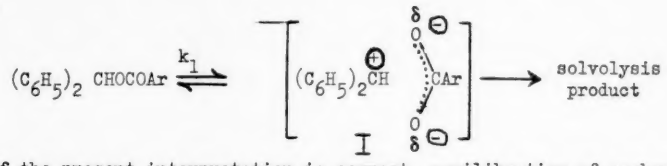
[6] S. Winstein, E. Clippinger, A.H. Fainberg, R. Heck and G.C. Robinson, J.Amer.Chem.Soc. 78, 328 (1956).

[7] It was shown earlier[2] that the rate of oxygen equilibration without rearrangement in an allylic system is sensitive to the ionizing power of the solvent which is consistent with the idea that the process involves internal return.

the oxygen atoms in I may not be completely equivalent and thus rates of ionization determined by this method are lower limits. Presumably the dissociated carbonium ion is an intermediate in the solvolysis-product forming step.



I

If the present interpretation is correct, equilibration of carboxyl oxygen atoms is an important method for detecting ion pair return because it is applicable in systems which do not rearrange. Moreover, optically active systems are not required. Except for detection of ion pair return by an "abnormal" salt effect[8] (which does not reveal internal return) methods used previously[9] are applicable only in systems which racemize or rearrange.[10]

Preliminary experiments[12] with optically active p-chlorobenzhydryl p-nitrobenzoate indicate that the intramolecular oxygen equilibration process is largely but not completely stereospecific (retention).[13]

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[8] S. Winstein, P.E. Klinedinst, Jr. and G.C. Robinson, J.Amer.Chem.Soc. 83, 885 (1961).

[9] For leading references see H.L. Goering, Rec.Chem.Progr. 21, 109 (1960).

[10] An important method for detecting ion pair return associated with the ionization of substituted benzhydryl chlorides has recently been developed by Winstein and coworkers.[11] This method involves comparison of rates of racemization and radio-chloride exchange and is applicable to systems which do not rearrange. However, optically active systems are required. Moreover, unlike with the present method, return with retention of configuration is not detected.

[11] S. Winstein, J.S. Gall, M. Hojo and S. Smith, J.Amer.Chem.Soc. 82, 1010 (1960); S. Winstein and J.S. Gall, Tetrahedron Letters No. 2, 31 (1960); S. Winstein, M. Hojo and S. Smith, Ibid. No. 22, 12 (1960); Y. Pocker, Proc.Chem.Soc. 140 (1961).

[12] Unpublished work by R.G. Briody.

[13] In ref. 2 it was reported that oxygen equilibration without rearrangement is stereospecific (retention) in a cyclic allylic system.

Tetrahedron Letters No. 18, pp. 648-653, 1961. Pergamon Press Ltd. Printed in Great Britain.

1961

THE PHOTODIMERS OF α-PYRIDONES

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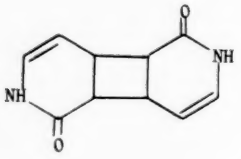
(Received 25 September 1961)

THE irradiation of α-pyridone has recently[1] been reported to give a dimer to which the structure (1) has been attributed. Related structures have been proposed[2] for dimers of uracil and thymine.



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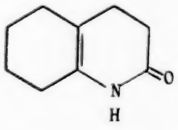

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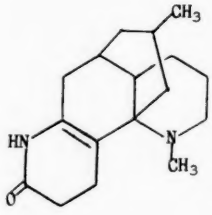

3

The structure (1) contains the system -C=C-N-CO. This system is

[1] E.C. Taylor and W.W. Paudler, Tetrahedron Letters No. 25, 1 (1960).

[2] S.Y. Wang, Nature, Lond. 190, 690 (1961).

present in 3,4,5,6,7,8-hexahydrocarbostyril[3] (2) and in α-obscurine[4] (3). These substances have absorptions with λ_{max} 253 (log ε 3.69) and λ_{max} 255 (log ε 3.73), respectively, in the ultraviolet. These observations are incompatible with the otherwise very reasonable structure proposed for α-pyridone dimer (1) since this, its N-methylated derivative and the other dimers described here have no such high intensity band in the ultra-violet. In the infra-red spectrum, furthermore, no band compatible with that to be expected from a vinyl lactam is to be found. These same facts also exclude from consideration the 1:2-1:4 Diels-Alder type adduct and strongly suggest that the dimer is formed by 1:4 addition of the dienic system to itself.

Experimental proof of the correctness of this was obtained in a simple manner. Irradiation of 4-methyl-N-methyl pyridone gave a dimer* [m.p. ca. 260° (dec.)]. If this were of the type (1) then the additional C-methyl substituent should be at a bridgehead. On the other hand if it were derived by 1:4 addition then it should be on a double bond. The NMR spectrum (doublet at 8.15τ) clearly indicates the latter to be correct. Furthermore, the ratio of vinyl to methine protons is now 1:2. The reverse argument obtains in the case of the dimer [m.p. 210-12° (dec.)] derived from the irradiation of 6-methyl-N-methyl pyridone. The position of the single band in the NMR (8.37τ), together with the fact that the ratio, vinyl:methine H is 2:1, indicates the quanternary nature of the methyl group. Since it has been shown[1] that N-methyl pyridone gives the same photodimer as obtained by the methylation of the pyridone dimer, and since it is well known[5] that alkylation of an ethylenic linkage is no impediment to the cyclobutane

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* Satisfactory analyses and molecular weights have been recorded.

3 A.D. Campbell and I.D.R. Stevens, J.Chem.Soc. 959 (1956).

4 W.A. Ayer and G.G. Iverach, Tetrahedron Letters No. 10, 19 (1960).

5 e.g. E. Zavarin, J.Org.Chem. 23, 47 (1958).

type of dimerization, the general nature of the pyridone dimer must be considered as established. It has analogy in the dimerization of anthracene.[6]

Four structures for the parent N-methylated dimer (4, A-D, R = R' = H, R'' = Me) are then possible. A study of the NMR spectrum suggests that A is correct, and this structure is also compatible with dipole moment measurements.[1]

The 60 Mc/sec spectrum (5% in $CDCl_3$) shows three groups of peaks: (a) 14 lines between 363.5 and 407.4 cps from TMS (olefinic protons), (b) a 16 line pattern from 205.3 to 249.0 cps (methine H's), and (c) a strong singlet at 168.1 cps (7.20τ, N-CH_3). Both (a) and (b) have the appearance of AB systems in which both the A and B bands are split by two additional spin-spin couplings. For the methine pattern, the chemical shifts for A and B are 215.4 cps (6.41τ) and 238.3 cps (6.03τ), respectively with J_{AB} = 10.0 cps. The chemical shifts for the olefinic protons are 372.2 cps (3.80τ) and 398.6 cps, (3.36τ), J_{AB} = 8.2 cps. The rest of the coupling constants are listed in Table 1.

Table 1

Coupling Constant for the Photodimers

(±0.1 cps)

Dimer of	$J_{36'}$*	J_{34}	J_{35}	J_{45}	J_{46}	J_{56}	$J_{5\text{-}CH_3}$
N-Me pyridone	10.0	6.4	1.4	8.2	1.6	6.6	-
N-Ac pyridone	10.6	6.8	1.6	8.3	1.6	7.0	-
N-Me-4-Me pyridone	10.1	-	2.1	-	-	6.8	1.7

* Numbering as in 4A

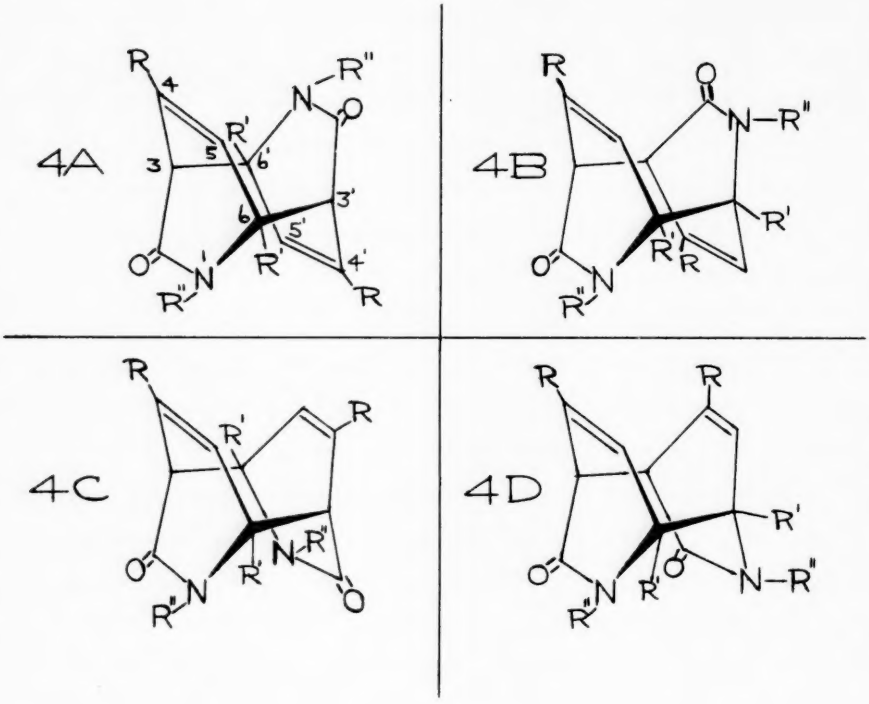
[6] D.E. Applequist et al., J.Am.Chem.Soc. 81, 457 (1959) and papers there cited.

Using Dreiding models, it is apparent that in 4A (R = R' = H; R'' = Me) the olefinic protons (on C_5,C_5') lie approximately over the >C = O grouping while the other two (on C_4,C_4') do not. This would lead to a difference in their respective chemical shifts. Furthermore, each of the methine protons is spin-spin coupled to <u>three</u> other nuclei. These two facts are compatible with the above observations and furnish support for the <u>trans-anti</u> formulation (A) over the other possibilities.

Apart from chemical shift differences, the N-$COCH_3$ (4, R = R' = H, R'' = Ac) dimer gives a similar spectrum (5% in $CDCl_3$). The methine protons appear at 4.64 and 6.19τ, while the olefinic H's are at 3.42 and 3.86τ. The coupling constants are listed in the table.

The spectrum (in $CDCl_3$) of the 4-methyl derivative 4 (R'' = R = Me, R' = H) is simplified. Since one of the olefinic protons has been replaced with methyl (doublet at 8.14τ, J = 1.7 cps), only 8 lines appear in the methine region. This pattern is, again, and AB system but each band is split by only one further interaction. The chemical shifts are A, 6.60τ, and B, 5.96τ and J_{AB} = 10.1, J_{AX} = 2.1 J_{BX} = 6.9 cps. The olefinic proton (3.75τ) appears as the expected multiplet for couplings of 6.9 and 2.1 cps with the methine protons and a weak coupling (J = 1.7 cps) with the neighbouring methyl group. It should be noted that the chemical shift of this proton corresponds closely to one of those in both the N-Me and the N-$COCH_3$ dimers. This proton (on C_5) is presumably slightly shielded by the neighboring C = O group. In this case, also, the dimer appears to be of the 4A type, which is compatible with dipole measurements (see below).

The NMR spectrum (in $CDCl_3$) of the 6, N-dimethyl derivative (4, R^1 = R^{11} = Me, R = H) is much simpler. In addition to singlets for N-CH_3 (7.20τ) and C-CH_3 (8.37τ), there are two lines in the olefinic region (396.0, 373.4



cps) and three in the methine region (189.5, 194.0, 198.5 cps). These results would suggest the exclusion of a structure of type 4A, since the olefinic protons are not greatly different.

Dipole measurements (in $CHCl_3$) indicate that the value for both the 4-methyl and the 6-methyl derivative is less than 2D.[7] Calculation indicates[7] that structures of type 4B and D should have dipoles greater than 4D. These results support the 4A type for the 4-methyl derivative, and, with the NMR evidence, suggest type 4C for the 6-methyl derivative.

[7] We are greatly indebted to Professor N.L. Allinger (Wayne) for these determinations and the calculations. We understand Professor Allinger will be reporting the dipole data in detail elsewhere.

Acknowledgements - We wish to thank Professor E.C. Taylor (Princeton) for a helpful discussion.

This work was supported by the U.S.A.F. under Grant No. AF-AFOSR-61-6, and by the National Research Council of Canada.

961

Tetrahedron Letters No. 18, p.654, 1961. Pergamon Press Ltd. Printed in Great Britain.

1961

ERRATA

ALAIN HOREAU: Principé et applications d'une nouvelle méthode de détermination des configurations dite "par dédoublement partiel", Tetrahedron Letters No. 15, 506-512 (1961).

The author has requested the following amendments to the above article.

1. Page 509, Tableau 1:

In the first column under "Substance" replace "6 Testostérone ou 17β-hydroxy 3-oxo pregna 4-ène" and "7 17α-hydroxy 3-oxo pregna 4-ène" by "6 Testostérone ou 17β-hydroxy 3-oxo androsta-4-ène" and "7 17α-hydroxy 3-oxo androsta-4-ène".

2. Page 511, eighth line:

The sentence beginning "Après 15 heures, ..." should now read "Après 15 heures, on ajoute une fine goutte d'eau et porte à 100° pendant 30 minutes, puis on verse dans un décanteur .....".

Tetrahedron Letters No. 19, pp. 655-657, 1961. Pergamon Press Ltd. Printed in Great Britain.

DIMETHYLCYCLOBUTENEDIONE

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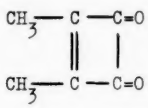
(Received 12 October 1961)

WE wish to report the synthesis of dimethylcyclobutenedione (dimethylcyclobutadienoquinone) (I), the first simple homolog of cyclobutenedione, several higher analogs of which have been previously reported.[1-4] All of these have side-chain unsaturation in conjugation with the cyclobutenedione system.



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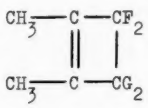

II

Methylation of perfluorocyclobutene[3] with methyl lithium in ether solution at -45°, an improvement of the general procedure described by Dixon[5], gave 1,2-dimethyltetrafluorocyclobutene (II) (55%); b.p. 100-104°, $n_D^{27.5}$ 1.3478. Hydrolysis[6] of compound II with 96-97% sulfuric acid at

1 E.J. Smutny and J.D. Roberts, J.Amer.Chem.Soc. 77, 3420 (1955).

2 M.P. Cava and D.R. Napier, J.Amer.Chem.Soc. 79, 3606 (1957).

3 A.T. Blomquist and E.A. LaLancette, J.Amer.Chem.Soc. 83, 1387 (1961).

4 C.M. Sharts and J.D. Roberts, J.Amer.Chem.Soc. 83, 871 (1961).

5 S. Dixon, J. Org.Chem. 21, 400 (1956).

6 J.D. Roberts, G.B. Kline and H.E. Simmons, Jr., J.Amer.Chem.Soc. 75, 4765 (1953).

65-70° for 70 min gave the diketone I (60%) as a yellow liquid; b.p. 74-76° (2 mm), n_D^{24} 1.4908. (Found: C, 65.41; H, 5.49; mol. wt., 127 (Rast). Calc. for $C_6H_6O_2$: C, 65.44; H, 5.49; mol. wt., 110.) Another reagent, polyphosphoric acid (PPA),[7] after 1.5 hr at 100-105° also hydrolyzed the fluorocarbon (II) to the diketone I (43%). A similar experiment with 100% orthophosphoric acid afforded only a poor yield of impure I; thus, it was indeed the unique properties of the reagent PPA which were responsible for the clean hydrolysis. These results serve to expand the versatility of PPA, since this is the first recorded case of its ability to hydrolyze gem-dihalo groups[8]. The ditosylhydrazone derivative of I had m.p. 190-191° (dec.). (Found: C, 53.71; H, 5.02; N, 12.60. Calc. for $C_{20}H_{22}O_4N_4S_2$: C, 53.70; H, 4.97; N, 12.55.) The controlled addition of 2,4-dinitrophenylhydrazine reagent[9] to I gave a mono-2,4-dinitrophenylhydrazone derivative; m.p. 205-208° (dec.). (Found: C, 49.68; H, 3.49; N, 19.45. Calc. for $C_{12}H_{10}N_4O_5$: C, 49.65; H, 3.47; N, 19.30.) The enedione I was soluble in water, ether, chloroform, benzene, dioxane, acetonitrile, and mineral acids. The compound could be stored in the refrigerator indefinitely, or at room temperature for several weeks without visible change.[10]

Reaction of compound I with aqueous 30-35% hydrogen peroxide at room

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7 The reagent was freshly prepared by the addition of 140 g of phosphorus pentoxide in 20 g portions to 90 ml of 85% orthophosphoric acid followed by a period of heating on the steam bath for 3-4 hr. Commercial reagent (Victor Chemical Co.) reacted much to vigorously at 100-105°, and no diketone I was obtained.

8a F.D. Pope and W.E. McEwen, Chem.Rev. 58, 321 (1958); b R.A. Raphael, E.C. Taylor and H. Wynberg, Advances in Organic Chemistry, Methods and Results Vol. I, pp.35-81. Interscience, New York (1960).

9 R.L. Shriner, R.C. Fuson and D.Y. Curtin, The Systematic Identification of Organic Compounds (4th. Ed.) p.219. John Wiley, New York (1956).

10 In aqueous solution, I underwent a photochemical reaction when exposed to direct sunlight or irradiated with a 275-Watt I.R.-U.V. sunlamp. A yellow, crystalline product with m.p. 222-223° was obtained which analyzed for the molecular formula, $C_{12}H_{12}O_4$. Elucidation of the structure of this dimer is in progress.

temperature readily gave dimethylmaleic anhydride (71%). The infra-red spectrum of I (neat) exhibited absorption characteristic of a strained carbonyl group attached to a four-membered ring at 5.60 and 5.67μ (unresolved doublet), with shoulders at 5.49 and 5.84μ; the first carbonyl overtone absorbed weakly at 2.83μ. Strong, sharp absorption at 6.21μ characteristic of an olefinic bond conjugated with a carbonyl group was also present. In the ultra-violet I (ethanol solution) showed the following maxima (ε's in parenthesis) characteristic of α-β unsaturated ketones:[11] 216 (18,800), 340 (26), and 355 mμ(shoulder) (23). In contrast to diphenylcyclobutenedione,[3] the diketone I showed fair stability in ethanol; the intensity of absorption of the compound in ethanol at 216 mμ decreased in 9 days to 13,500 and in 16 days to 12,080. The diphenyl analog in ethanol deteriorated completely within 12 hr to give a mixture of meso and racemic diethyl α,α'-diphenylsuccinate.

The NMR proton spectrum showed only one unresolved peak at 2.40 p.p.m. to lower field than the resonance of protons in an internal tetramethylsilane standard. In comparison, the NMR spectrum of biacetyl showed a similar single, unresolved peak at 2.25 p.p.m. lower than the standard.

Acknowledgement - This investigation was supported by a research grant from the B.F. Goodrich Company, for which the authors are deeply grateful.

[11] A.E. Gillam and E.S. Stern, An Introduction to Electronic Absorption Spectroscopy in Organic Chemistry (2nd Ed.) pp.103-107. E. Arnold, London (1957).

Tetrahedron Letters No. 19, pp.658-662, 1961. Pergamon Press Ltd. Printed in Great Britain.

A TETRA-t-BUTYLBENZENE

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(Received 18 September 1961; in revised form 9 October 1961)

THERE has been considerable speculation about the properties that might be expected of aromatic compounds substituted with large groups in positions ortho to each other. In particular, o-di-t-butylbenzene has been the subject of some discussion[2,3] and of several synthetic attempts which have so far been unsuccessful.[4,5] We have attempted to approach this problem through the cyclization of appropriate acetylenic compounds with organometallic catalysts. While we were engaged in this work Hübel and Hoogzand[6] mentioned the preparation of 1,2,4-tri-t-butylbenzene using an organo-cobalt carbonyl complex. We describe below the formation of a compound which is in all probability 1,2,4,5-tetra-t-butylbenzene from the reaction of mono-t-butyl acetylene with the mono-adduct of di-t-butyl acetylene and dicobalt octacarbonyl. Independent experiments which will be described elsewhere

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[1] U.S. Bureau of Mines, Bruceton, Pennsylvania.

[2] H.C. Brown and K.L. Nelson, J.Amer.Chem.Soc. 75, 24 (1953).

[3] H.C. Brown, D. Gintis and L. Domash, J.Amer.Chem.Soc. 78, 5387 (1956).

[4] E.M. Arnett, J.Org.Chem. 25, 324 (1960).

[5] L.R.C. Barclay, N.D. Hall and J.W. MacLean, Tetrahedron Letters No. 7, 243 (1961).

[6] W. Hubel and C. Hoogzand, Chem.Ber. 93, 103 (1960).

indicate that o-di-t-butylbenzene may also be made in the same fashion. It is interesting that although 1,2,4,5-tetra-t-butylbenzene must be highly strained, its spectral properties do not indicate that its aromatic character has been dramatically affected.

The mono-adduct[7,8] of di-t-butylacetylene[9] and dicobalt octacarbonyl was prepared by mixing the two compounds at room temperature in Skellysolve F as solvent. Within 1½ hr the expected two equivalents of carbon monoxide had been evolved and upon removal of solvent a red-brown solid was obtained which was purified by sublimation (103°/1.5 mm) to give an 81.3% yield of ruby needles decomposing at 220° (uncorr.) in a sealed tube. In accordance with the formula $[(CH_3)_3C\text{-}C\equiv C\text{-}C(CH_3)_3]Co_2(CO)_6$ the infra-red spectrum showed the usual t-butyl bands and also the three terminal carbonyl bands at 4.83, 4.92 and 4.98μ which are customary for acetylenic mono-adducts of dicobalt octacarbonyl.[7,8] The 5.38μ band for the bridging carbonyl groups in $Co_2(CO)_8$ was absent. [(Schwarzkopf. Found: C, 45.54, 45.53; H, 4.24, 4.47; Co, 27.82, 28.13. Calc. for $C_{16}H_{18}O_6Co_2$: C, 45.30; H, 4.28; Co, 27.75].

The mono-adduct described above was refluxed with six equivalents of mono-t-butylacetylene (b.p. 35°) in Skellysolve C at 95° under a Dry-Ice condenser attached to a gas burette. After 6 hr the theoretical amount (two equivalents) of carbon monoxide had been evolved; at this point the bulk of the solvent was removed by distillation. The concentrated liquor was chromatographed on alumina and eluted with Skellysolve F. The first band to be discharged was a brown one which owed its color to unreacted

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7 H. Greenfield, Ph.D. Thesis, University of Pittsburgh (1955).

8 H. Greenfield, H.W. Sternberg, R.A. Friedel, J.H. Wotiz, R. Markby and I. Wender, J.Amer.Chem.Soc. 78, 120 (1956).

9 G.F. Hennion and T.F. Branigan, Jr., J.Amer.Chem.Soc. 68, 1202 (1946).

mono-adduct as shown by infra-red analysis. Immediately following this was a purple fraction whose color may have been due to a cobalt carbonyl tri-adduct although this was not demonstrated. Evaporation of solvent from these two fractions precipitated white crystals melting at 159.6° (uncorr.) in a sealed tube (on a Fisher-Johns block they sublimed). Gas chromatography showed the presence of a single component. Determination of the molecular weight by low-ionization voltage mass spectrum showed a main peak at mass 302, which could correspond to a tetra-t-butylbenzene, and a second smaller peak at 15 mass units less indicating fragmentation of a methyl group from the original molecule. [(Schwarzkopf). Found: C, 87.21, 87.51; H, 12.78, 12.82. Calc. for $C_{22}H_{38}$: C, 87.34; H, 12.66] The yield was 18.5% after recrystallization from methanol.

The compound then is most likely a tetrabutylbenzene and, by virtue of the synthetic route, is probably one of the three possible tetra-t-butyl-benzenes. Evidence that it is the 1,2,4,5-isomer rather than the 1,2,3,4- or the 1,2,3,5-compounds rests mostly on the following spectral observations

The NMR spectrum showed only two sharp peaks in approximately the proper ratio of 18:1. This not only supports the fact that the aliphatic hydrogens are all in t-butyl groups but argues for the compound being the most symmetrical of the three isomers. Examination of the NMR results for the three tetramethylbenzenes shows the 1,2,4,5-isomer to be the only one with two simple unsplit peaks.

The ultra-violet spectrum (Cary-14 using cyclohexane as solvent) showed a single rounded peak at 273 mμ (ϵ = 363). The disappearance of fine structure is typical of highly strained aromatic systems. In Table 1 are presented the important bands and extinction coefficients for the three tetramethylbenzenes and 1,2,4,5-tetra-i-propylbenzene. It is seen that

1,2,4,5-tetramethylbenzene has an outstandingly stronger absorbance at all three bands than do the other two tetramethyl isomers. The corresponding tetra-i-propylbenzene has three bands in the same position but all of them, especially the one at 271.5 mμ, are reduced in absorbance. The single band of the tetra-t-butyl compound does not have as great an intensity as the bands of 1,2,4,5-tetra-i-propylbenzene and the fact that the single band in tetra-t-butylbenzene absorbs more strongly than do any of the bands for 1,2,3,4- or 1,2,3,5-tetramethylbenzenes is strong circumstantial evidence for the compound being 1,2,4,5-tetra-t-butylbenzene.

Table 1

Substituted benzene	λ, mμ	ε
1,2,3,4-Tetramethyl	268	292
	272	216
	277	211
1,2,3,5-Tetramethyl	268.5	273
	273.5	230
	277	207
1,2,4,5-Tetramethyl	269	625
	272	568
	278	666
1,2,4,5-Tetra-i-propyl	268	594
	271.5	436
	277	654
Tetra-t-butyl	273	363

Interpretation of the infra-red data is made rather tenuous by the scarcity of literature on tetra-substituted benzenes; however, the following tabulation of long wavelength bands gives permissive evidence for the 1,2,4,5-structure and argues against the 1,2,3,4-arrangement. The frequency for out-of-plane aromatic C-H vibrations in poly-substituted benzenes is supposed to be relatively insensitive to the nature of groups attached to

the nucleus and mainly determined by the substitution pattern.[10] If the longest wavelength band for the compounds in Table 2 may be assigned to this vibration, the position of the bands for our compound appears to support the 1,2,4,5-arrangement. However, at present, assignments for such highly substituted systems are risky.[10] The rest of the spectrum showed the expected bands including the usual ones for t-butyl groups.

Table 2

Substituted benzene	Long wavelength band (cm^{-1})
1,2,3,4-Tetramethyl (in CS_2)	730 (w-m) 805 (vs)
1,2,3,5-Tetramethyl (in isooctane)	706 (s) 738 (m) 850 (vs)
1,2,4,5-Tetramethyl (in isooctane)	868 (vs)
1,2,4,5-Tetrafluoro (film)	852) (vs) 870) (vs)
Tetra-t-butyl (in CCl_4)	888 (m)

Acknowledgements - We are grateful to the National Science Foundation for a grant NSF-G-14583 supporting this work. We wish to express our great appreciation to Dr. B. Blaustein, Mr. A. G. Sharkey, Jr., Miss Janet Shultz and Mr. Sol Metlin, all of the U.S. Bureau of Mines, for assistance in this work. We thank Dr. A.A. Bothner-By of Mellon Institute for obtaining and interpreting the NMR spectrum.

10 L.J. Bellamy, The Infra-red Spectra of Complex Molecules (2nd Ed.) p.79. John Wiley, New York, (1958).

Tetrahedron Letters No. 19, pp. 663-665, 1961. Pergamon Press Ltd. Printed in Great Britain.

ON HECTOR'S BASE

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Organic Chemistry Research Section, Banaras Hindu University

(Received 29 September 1961)

THE new structure (VIII) is suggested for Hector's base from a consideration of its conversion into the isomer (IV) and synthesis from (VII).

Phenyl thiocarbamide by its oxidation in acidic aqueous or alcoholic solutions is known to form a base $C_{14}H_{12}N_4S$, m.p. 181°, first obtained by Hector[1] who assigned its structure (I): 3,5-diimino-2,4-diphenyl-1,2,4-thiadiazolidine. Dost[2] by heating Hector's base with (i) fuming hydrochloric acid and (ii) alcoholic ammonia obtained a non-basic compound $C_{14}H_{11}N_3SO$ and another base isomeric with Hector's base, respectively. He also obtained diphenylguanidine as one of its reduction products. Dost on his evidence favoured structure (II) while Lal and Krall[3] who carried out several unfruitful attempts towards its synthesis thought that structure (III) could not be precluded from consideration. Kurzer[4,5] has shown recently that the isomeric base obtained by Dost was really 3,5-diphenylimino-1,2,4-thiadiazolidine (IV) and opined that the structure (I) initially assigned

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[1] D.S. Hector, Ber.Dtsch.Chem.Ges. 22, 1176 (1889). For other references K.B. Lal and H. Krall, J.Indian.Chem.Soc. 16, 31 (1939); K.S. Suresh, J. Sci. Res. Banaras Hindu Univ. IX (2), 94 (1958/59); Ph. D. Thesis, Banaras Hindu University.

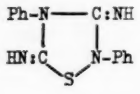
[2] K. Dost, Ber.Dtsch.Chem.Ges. 39, 863 (1906).

[3] K.B. Lal and H. Krall, J.Indian.Chem.Soc. 16, 31 (1939).

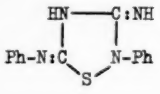
[4] F. Kurzer, Chem. & Ind. 526 (1956).

[5] F. Kurzer, J.Chem.Soc. 2345-52 (1956).

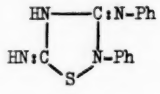
for the base probably represented it correctly.



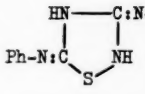
I



II



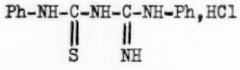
III



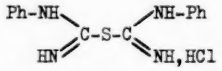
IV

We have now found that when Hector's base is reduced with ammonium hydrogen sulphide diphenylguanidine and thiocyanic acid are produced almost quantitatively. This again favoured structure (I) but excluded (II). We have been able to synthesize Hector's base by the following sequence of changes.

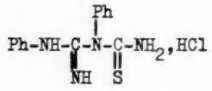
Phenylcyanamide was condensed with phenylthiocarbamide in ether acetone mixture in presence of hydrochloric acid when a colourless hydrochloride $C_{14}H_{14}N_4S$, HCl m.p. 158° of a base (VII) was obtained. This was found different from the other expected likely isomeric products (V) and (VI): The N-phenylformamidino-N'-phenylthiocarbamide (V)[5] was already known and as judged from its properties and absence of yellow colour it could also not be assigned the structure of isomeric diphenylformamidine monosulphide (VI).[6]



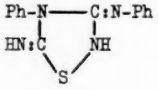
V



VI



VII



VIII

On oxidation of VII with hydrogen peroxide (bromine and iodine also) Hector's base was obtained quantitatively.

This route of its formation, however, could lead to 3-phenylimino-4-

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[6] cf. K.S. Suresh, J.Indian.Chem.Soc. 37,483 (1960).

phenyl-5-imino-1,2,4-thiadiazolidine (VIII) or to Hector's originally suggested structure (I). Since (I) is not convertible into (IV) by a simple isomeric change as observed by Dost and Kurzer (loc.cit.) and confirmed by us now in the case of this and other Hector's bases also, we prefer structure (VIII) for this compound. A rupture of the C—N bond between positions 3 and 4 followed by an interchanging of positions of :NH and N-Ph in positions 5 and 4 respectively and reformation of C—N bond would convert (VIII) into (IV). This is supported by our observation that the corresponding C—N bond in (VII) and in 5-phenylimino-4-phenyl-3-thion-1,2,4-dithiazolidine and in 5-phenylimino-4-phenyl-3-imino-1,2,4-dithiazolidine is prone to easy disruption when heated with an amine or ammonia.

Sincere thanks of the authors are due to Dr. R.H. Sahasrabudhey for his interest.

Tetrahedron Letters No. 19, pp. 666-668, 1961. Pergamon Press Ltd. Printed in Great Britain.

1961

DIE ÜBERFÜHRUNG VON 16α:17α-EPOXY-PREGNENOLON IN DAS 3β:16α-DIHYDROXY-$\Delta^{5,17(20)}$-5-17-PREGNADIEN DURCH DIE MODIFIZIERTE KISHNER-WOLFF-REDUKTION

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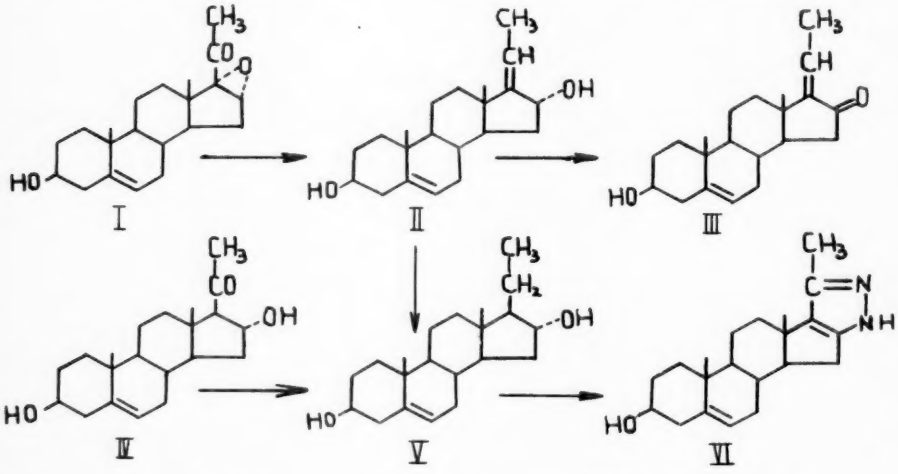
(Received 18 August 1961; in revised form 18 October 1961)

DIE 16α:17α-Epoxyverbindung (1)[1] geht in guter Ausbeute durch modifizierte Kishner-Wolff-Reduktion[2] in die 16α-Hydroxyverbindung über, deren Konstitution durch folgende experimentelle Ergebnisse als II bewiesen werden konnte:



In den I.R.-Spektren von II (Schmp. 182-183°, $[\alpha]_D^{27}$ -89° (Äthanol)) und seinem Diacetat (Schmp. 158-160°, $[\alpha]_D^{27}$ -67° (Äthanol)) zeigen nicht

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[1] P.L. Julian, E.W. Meyer, J. Kappel und I.R. Waller, J.Amer.Chem.Soc. 72, 5145 (1950).

[2] Huang-minlon, J.Amer.Chem.Soc. 68, 2487 (1946); Huang-minlon, Chung-Tungshun, Ku-Tusing und Chow-Weizan, Acta.Chem.Sinica, 238 (1957).

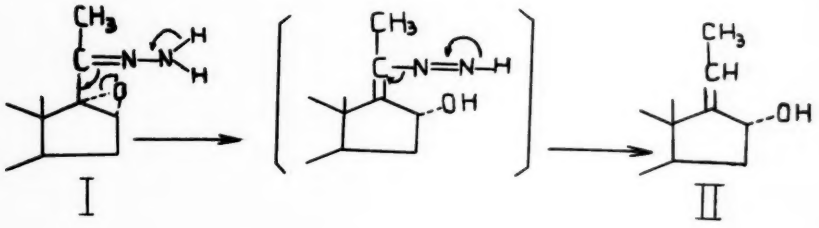
mehr die Absorptionsbanden der Ketogruppe. Erwartungsgemäss konnten keine OH-Absorptionbanden im Spektrum des Diacetates beobachtet werden.

Diese Verbindung (II) liefert durch Schütteln mit MnO_2 eine konjugierte Ketoverbindung (III; Schmp. 164-166°, $[\alpha]_D^{23}$ -219° (Äthanol), λ_{max}: 245 mμ log ε 3.91), wodurch also die Anwesenheit und die Lage der Doppelbindung und der Hydroxygruppe im Ring D nachgewiesen wurden.

Zur weiteren Strukturbestätigung haben wir die 16α-Hydroxyverbindung (II) mit Pd-$CaCO_3$ als Katalysator selektiv hydriert und eine Dioxyverbindung (V; Schmp. 240-251°, $[\alpha]_D^{27}$ -73° (Äthanol)) erhalten, welche mit dem aus der bekannten Verbindung (IV)[3] durch modifizierte Kishner-Wolff-Reduktion erhaltenen Produkt (Schmp. 240-241°) identisch ist.

Der Mischschmp. der Diacetate von V (Schmp. 158-159°, $[\alpha]_D^{27}$ -143° (Äthanol)) und II ist erniedrigt.

Bemerkenswert ist, dass man zur Darstellung von V aus IV das Alkali erst nach der Bildung des Hydrazons zum Reaktionsgemisch zugeben muss, um β-Elimination der 16-Oxygruppe zu vermeiden. Aus dem rohen Reduktionsprodukt (II) wurde noch eine Stickstoffhaltige Verbindung in geringer Menge isoliert,



I II

[3] S. Berstein, M. Heller und S.M. Stolar, J.Amer.Chem.Soc. 76, 5674 (1954).

[4] Huang-minlon, J.Amer.Chem.Soc. 71, 3301 (1949); O.N. Witt und O. Braun, Ber.Dtsch.Chem.Ges. 47, 3216 (1914).

welche nach ihrer Analyse und den analogen Ergebnissen, die bei der Reduktion von β-Ketolverbindungen beobachtet worden sind,[4] wahrscheinlich als ein Pyrazolinverbindung (VI; Schmp. 302-304°, $[\alpha]_D^{27}$ -76° (Chloroform)) angesehen werden kann.

Die Entstehung der Verbindung II als I ist sehr leicht erklärlich durch das folgende Reaktionsschema.

Tetrahedron Letters, No. 19, pp. 669-675, 1961. Pergamon Press Ltd. Printed in Great Britain.

ACID-CATALYZED ISOMERIZATION AND CLEAVAGE OF DIOXIMES OF THE PHOTODIMERS OF γ-PYRONES

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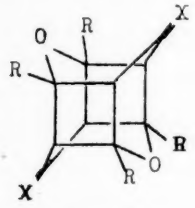
Department of Chemistry, Harvard University,

Cambridge, Mass.

(Received 4 October 1961)

IN the course of studies on the chemistry of cage ketones of type I we have investigated the reactions of the corresponding dioximes, II, in strongly acid media. In no case were Beckmann rearrangement products obtained, but the reactions followed alternative pathways of some interest and novelty.

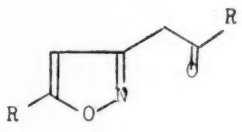


Ia R=CH_3, X=O

Ib R=C_2H_5, X=O

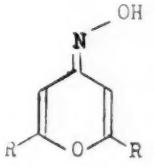
IIa R=CH_3, X=NOH

IIb R=C_2H_5, X=NOH



IIIa, R=CH_3

IIIb, R=C_2H_5



IVa, R=CH_3

IVb, R=C_2H_5

Brief treatment of IIa, dec. 305° (evac. cap.), the dioxime[2] of Ia[3],

[1] Present address: Department of Chemistry, University of Toronto.

[2] This material is apparently a single stereoisomer, for it is converted to a single diacetate (cf. the case of IIb, below[10]).

[3] P. Yates and M.J. Jorgenson, J.Amer.Chem.Soc. 80, 6150 (1958).

with concentrated sulfuric acid on the steam bath gives three products, a colorless liquid, $C_7H_9O_2N$ [Found: C, 60.50; H, 6.46; N, 10.00; M.W. (Rast) 150], colorless needles, $C_7H_9O_2N$, m.p. 124-124.5° (Found: C, 60.63; H, 6.53; N, 10.35), and colorless needles[4], $C_{14}H_{18}O_4N_2$, m.p. 122-122.5° [Found: C, 60.51; H, 6.55; N, 10.29; M.W. (isothermal dist.) 250]. The liquid product, λ_{max}^{liq} 3.18, 5.82, 6.22, 6.77 and 7.40μ, λ_{max}^{EtOH} 218mμ (ϵ5700), τ (liq.) 4.00, 6.22, 7.72, 7.90 p.p.m. with area ratio ca. 1:2:3:3, forms a p-nitrophenylhydrazone, $C_{13}H_{14}O_3N_4$, m.p. 125-126°, λ_{max}^{EtOH} 218 mμ (infl., ϵ14,500), 250 mμ (ϵ13,000), and 384 mμ (ϵ28,000) (Found: C, 57.08; H, 5.27; N, 20.79), and gives a positive iodoform test. On the basis of these data and comparison of its spectra with those of model compounds, this product is assigned structure IIIa, confirmed by its independent synthesis by the oxidation of 3-(2-hydroxypropyl)-5-methylisoxazole, λ_{max}^{liq} 2.95, 3.18 and 6.22μ, λ_{max}^{EtOH} 216 mμ (ϵ4600) (Found: C, 59.40; H, 8.03; N, 10.16), itself prepared by reaction of 2,3-dihydro-2,6-dimethyl-4-pyrone[5] with hydroxylamine hydrochloride and pyridine followed by treatment with acid. The crystalline product m.p. 124-124.5°, has the following spectral properties: $\lambda_{max}^{CHCl_3}$ 2.76, 3.05 (br), 5.90 and 6.14μ, λ_{max}^{EtOH} 261 mμ (ϵ15,000), τ($CDCl_3$) 0.02, 3.54, 4.16 and 7.87 p.p.m. with area ratio ca. 1:1:1:6. It forms an acetate $C_9H_{11}O_3N$, m.p. 128.5-129.5°, $\lambda_{max}^{CHCl_3}$ 5.70, 5.94, 6.18 and 6.37μ, λ_{max}^{EtOH} 214 mμ(ϵ7500) and 266 mμ (ϵ16,900) [Found: C, 59.87; H, 6.05; N, 7.46; M.W. (Rast) 179], and is converted to 2,6-dimethyl-4-pyrone in poor yield on hydrolysis with hot dilute sulfuric acid in the presence of formaldehyde. On the basis of

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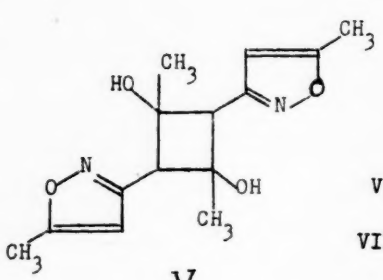
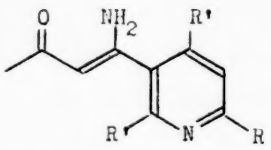
[4] Cf. M.J. Jorgenson, Ph.D. Thesis, Radcliffe College, 1959.

[5] Prepared by partial hydrogenation of 2,6-dimethyl-4-pyrone over Pd/$CaCO_3$ followed by separation from accompanying reduction products by distillation and chromatography: cf. J.J. de Vrieze, Rec.Trav.Chim. 78, 91 (1959).

these data it is assigned structure IVa, confirmed by its independent synthesis by the action of hydroxylamine hydrochloride and sodium carbonate on 2,6-dimethyl-4-thiopyrone. The crystalline product, m.p. 122-122.5°, has the following spectral properties: λ_{max}^{Nujol} 2.81, 2.86, 3.17, 6.25μ, λ_{max}^{EtOH} 218 mμ (ϵ12,500), τ($CDCl_3$) 3.87, 6.00, 6.60, 7.60 and 8.50 p.p.m. with area ratio ca. 1:1:1:3:3. It is rapidly converted to compound IIIa by the action of hot aqueous 10% sodium hydroxide and by gentle heating above its m.p., attempted acetylation with acetic anhydride and pyridine on the steam bath for 2 hr gives a mixture of IIIa and starting material. Consideration of these data and rational routes for the acid-catalyzed isomerization of IIa (vide infra) leads to the assignment of structure V to the compound, m.p. 122-122.5°. Hydrogenation of V in acetic acid over platinum gives a colorless oil, $\lambda_{max}^{CHCl_3}$ 2.88, 2.99, 3.07, 3.16 (sh), 6.18, 6.28, 6.42 and 6.58μ, which forms a crystalline acetyl derivative, $C_{16}H_{22}O_3N_2$, m.p. 102.5-103°, $\lambda_{max}^{CHCl_3}$ 2.87, 3.0 (br), 5.79, 6.18, 6.29, 6.42 and 6.59μ, λ_{max}^{EtOH} 275mμ(infl. ϵ8000) and 304 mμ (ϵ20,500) (Found: C, 66.14; H, 7.49; N, 9.41). The hydrogenation product and its acetyl derivative are formulated as VI and VII, respectively, on the basis of this and the following evidence. Dehydration of VI with concentrated sulfuric acid gives VIII, m.p. 125.5-128.5° (resolidifies 129°, remelts 131°), $\lambda_{max}^{CHCl_3}$ 2.84, 3.06, 6.03, 6.14 (sh), 6.17, 6.28 and 10.36μ, λ_{max}^{EtOH} 246mμ (ϵ12,200) and 303mμ (ϵ27,000), τ($CDCl_3$) 0.00, 3.07, 3.52 (multiplet), 5.00, 7.60, 7.75, 8.02 and 8.17 p.p.m. with area ratio of last five peaks ca. 2:6:6:9:3 [Found: C, 72.85; H, 8.08; N, 11.91; pk_a' (50% EtOH/H_2O) 4.95]. Hydrogenation of VIII in ethanol over Pd/C gives the dihydro compound IX, m.p. 113-115° (resolidifies, remelts 130°), $\lambda_{max}^{CHCl_3}$ 2.84, 3.05, 6.16, 6.28, 6.40 and 6.55 (br)μ, λ_{max}^{EtOH} 275mμ (infl., ϵ 8400) and 303mμ (ϵ20,000), τ($CDCl_3$) 0.72 (br), 3.32, 3.82 (br), 5.12, 7.55, 7.72, 8.05 (superimposed on other, broad bands) and 9.07



V



VI, R= $CH_2CHOHCH_3$, R'=CH_3

VII, R= $CH_2\underset{OCOCH_3}{CH}CH_3$, R'=$CH_3$

VIII, R=CH=$CHCH_3$, R'=CH_3

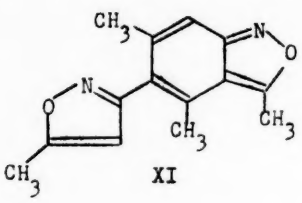
IX, R=$CH_2CH_2CH_3$, R'=CH_3

X, R=R'=H

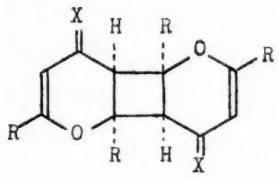
(triplet, J=6 c./s.) p.p.m. [Found: C, 72.56; H, 8.65; N, 12.25; pK_a' (50% EtOH/H_2O) 5.35] [cf. X[6]: $\lambda_{max}^{CHCl_3}$ 2.84, 3.05, 6.14, 6.26, 6.40 and 6.57μ λ_{max}^{EtOH} 225mμ (ε 8000), 248mμ (ε 6000) and 325mμ (ε 14,000), τ($CDCl_3$) 0.50 (br), 1.37 (doublet, J ~ 1 c/s), 1.57 (quartet), 2.25 (multiplet), 2.86 (multiplet), 3.25 (br), 4.65 and 7.95 p.p.m.].

Brief treatment of the dioxime IIa with polyphosphoric acid at 110° gives IIIa and V as the major products together with a product $C_{14}H_{14}O_2N_2$, m.p. 109-110.5°, $\lambda_{max}^{CHCl_3}$ 6.10, 6.24 and 6.37μ, λ_{max}^{EtOH} 210mμ (app., ε 42,000), 318mμ (ε 6100) and a series of peaks at 260-290mμ, τ($CDCl_3$) 2.90, 4.02, 7.17, 7.52, 7.70 and 7.92 p.p.m. with area ratio ca. 1:1:3:3:3:3 [Found: C, 69.03; H, 5.99; N, 11.07; M.W. (Rast) 255]. This compound can also be obtained in low yield by treatment of IIIa with polyphosphoric acid at 110-117° for 45 minutes and is assigned structure XI [cf. 3-methylanthranil: $\lambda_{max}^{CHCl_3}$ 6.08, 6.20, 6.33 and 6.39μ, ϵ_{210}^{EtOH} 12,000, λ_{max}^{EtOH} 316mμ (ε 5800) and a series of peaks at 245-280mμ, τ($CDCl_3$) 2.75 (multiplet) and 7.27 p.p.m.].

[6] Compound X, m.p. 92-93° (Found: C, 66.66; H, 6.32; N, 16.89), was prepared by treatment of 3-cyanopyridine with the sodium derivative of acetone in tetrahydrofuran.



XI



XIIa, R=CH_3, X=NOH

XIIb, R=C_2H_5, X=NOH

XIIIa, R=CH_3, X=O

XIIIb, R=C_2H_5, X=O

These observations can best be interpreted in terms of a reaction scheme in which the dioxime IIa is first converted by cleavage of one of its cyclobutane rings to an intermediate, XIIa; the breaking of the two C-C bonds may be formulated as occurring via protonation on nitrogen followed by retroaldol type bond fission.[7] Cleavage of the remaining cyclobutane ring in XIIa in like fashion would lead to the oxime IVa.[8] Compound XIIa could also serve as the source of V and IIIa via acid-catalyzed cleavage of both of its enol ether functions; cyclization of the resulting intermediate would then give V, while retroaldol type fission followed by cyclization could give IIIa (and also IVa). Routes to IIIa via IVa or V are unlikely since IVa and V do not give rise to IIIa under the conditions of the original reaction. The formation of XI can readily be formulated in terms of the self-condensation of IIIa.

Considerable strength is lent to the postulation of the intermediacy

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[7] Cf. C.A. Grob and W. Baumann, Helv.Chem.Acta. 38, 594 (1955).

[8] Cf. the acid-catalyzed reversion of Ia to 2,6-dimethyl-4-pyrone.[3]

of XIIa by the results of a study of the reaction of dioxime IIb,[9,10] m.p. 263-267° dec. (Found: C, 64.61; H, 7.78; N, 8.42) with concentrated sulfuric acid. Under the same conditions as those used with IIa, four products are obtained. Two of these are analogous to products obtained from IIa: compound IIIb, a colorless liquid, λ_{max}^{liq} 5.81 and 6.24μ, λ_{max}^{EtOH} 217mμ(ε6600) (Found: C, 64.82; H, 7.67; N, 8.35) and compound IVb, m.p. 69.5-70.5°, $\lambda_{max}^{CHCl_3}$ 2.75, 3.05 (br), 5.93 and 6.17μ, λ_{max}^{EtOh} 265mμ(ε12,500) (Found: C, 64.17; H, 7.97; N, 8.16). The other two products, m.p. 212° dec, λ_{max}^{Nujol} 3-4, and 6.10μ, λ_{max}^{EtOH} 264mμ(ε33,600) (Found: C, 64.52; H, 7.69; N, 8.37) and m.p. 192.5-193°, λ_{max}^{Nujol} 3-4, 6.05 and 6.14 (sh)μ, λ_{max}^{EtOH} 263mμ(34,000) (Found: C, 64.79; H, 7.75; N, 8.22), are considered to be stereoisomers of structure XIIb: their spectra may be compared with those of XIIa, m.p. 218-220° dec., λ_{max}^{Nujol} 3-4, 6.02 (sh) and 6.08μ, λ_{max}^{EtOH} 262mμ(ε29,200) (Found: C, 60.13; H, 6.64; N, 9.81), prepared by the action of hydroxylamine on XIIIa, itself obtained by pyrolysis of Ia.[4] No product analogous to V is detected in the reaction of IIb with sulfuric acid or with polyphosphoric acid; the latter reagent gives rise to the same products as those obtained with sulfuric acid.

It is therefore proposed that the acid-catalyzed reactions of both IIa and IIb lead first to a compound of type XII; in the case of XIIa, this is rapidly converted to IIIa, IVa and V, while in the case of XIIb, it is more slowly converted to IIIb and IVb only.[11] The difference in behavior in the

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9 The parent diketone, Ib, m.p. 261-262° dec. (Found: C, 70.94; H, 7.94) was prepared by irradiation of 2,6-diethyl-4-pyrone.

10 This material is probably a mixture of two stereoisomeric forms of IIb since on acetylation it gives two diacetates, differing in the fingerprint region of their solution infra-red spectra but possessing superimposable nuclear magnetic resonance spectra.

11 A related difference in behaviour of the diketones Ia and Ib has recently been observed: under conditions which suffice to bring about the acid-catalyzed reversion of Ia to monomer,[3] IIb yields XIIIb in high yield. (P. Yates and S.K. Roy, unpublished results.)

case of XIIb may be attributed to a combination of the following factors; enhanced steric hindrance to solvation of charged intermediates in the cyclobutane ring cleavage process and to nucleophilic attack in the enol ether cleavage process, and increased unfavorable trans-annular interactions.

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THE CONFORMATION OF RING A IN 4,4-DIMETHYL-3-KETO-STEROIDS[1,2]

Norman L. Allinger and Margaret A. DaRooge[3]

Department of Chemistry, Wayne State University, Detroit 2, Michigan

(Received 3 October 1961)

THE ground state conformations of the steroid ring systems are in general securely locked in potential wells, can vary but little, and are for the most part well understood. In a 4,4-dimethyl-3-keto-5α-steroid (I) however, there is reason to question whether or not ring A will be in the standard chair form, and the answer to this question is of interest because of the widespread occurrence of this type of structure in nature. Recently, numerical values have been reported for the enthalpies of two quantities related to this question, namely the 1,3-diaxial dimethyl interaction,[4] 3.7 kcal/mole, and the chair→boat transformation of a cyclohexanone,[5] 2.8 kcal/mole. Actually other interactions must be considered, but a first approximation would seem to indicate that ring A in I might be more comfortable in the boat form than in the undeformed (or slightly deformed) chair (II).

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[1] Conformational Analysis XXII. For the preceding paper see N.L. Allinger and S. Hu, J.Amer.Chem.Soc. In press.

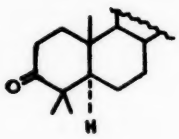
[2] This work was supported in part by Grant No. E-2267 from the Public Health Service, National Institutes of Health.

[3] Predoctoral U.S. Public Health Service Fellow, General Division of Medical Sciences, 1960-62.

[4] N.L. Allinger and M.A. Miller, J.Amer.Chem.Soc. 83, 2145 (1961).

[5] N.L. Allinger and H.M. Blatter, J.Amer.Chem.Soc. 83, 994 (1961).

An examination of models indicates that the boat form under consideration has a certain amount of flexibility, and the most stable arrangement may be either of two extremes, III or IV, or it may be somewhere in between.

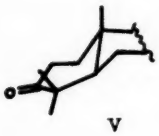


I

II

III

IV



V

Another possibility must also be considered, which is V. Here C-3 is moved upward (relative to II) approximately to the plane defined by carbons 1,2,4 and 5. Such a structure is similar to the transition state between boat and chair forms, which for cyclohexanone can be estimated roughly as the sum of two "half-eclipsed" ethanes (3 kcal) plus two acetone barriers (perhaps 2 kcal).[6] The energy of this distorted chair (5 kcal/mole) is therefore comparable in magnitude to the other possibilities and must also be considered.

The non-chair structure for 3-ketones is commonly represented as III.[7,8,9] A general objection to this arrangement is that it contains two eclipsed ethanes (6 kcal), while a boat type IV contains but one (3 kcal).

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[6] J.D. Swalen and C.C. Costain, J.Chem.Phys. 31, 1562 (1959).

[7] D.H.R. Barton, D.A. Lewis and J.F. McGhie, J.Chem.Soc. 2907 (1957).

[8] C. Djerassi, N. Finch, R.C. Cookson and C.W. Bird, J.Amer.Chem.Soc. 82, 5488 (1960).

[9] F. Sondheimer, Y. Klibansky, Y.M.Y. Haddad, G.H.R. Summers and W. Klyne, J.Chem.Soc. 767 (1961).

Offsetting this difference in IV, the latter has a 1,3-diaxial dimethyl interaction which in III is lacking. Something in between III and IV can probably minimize the total energy of a boat form by having each of these unfavourable effects present to a small degree.

In an effort to obtain a decision as to the conformational structure of ring A, a series of dipole moments were measured for the compounds listed in Table 1. Compounds (1) through (4) and (7) were all obtained by standard methods and had properties in good agreement with the literature values. Compounds (5), m.p. 138°, and (6), m.p. 134°, were obtained by oxidation of the known 17 alcohols [10,11] and gave proper analyses.

Table 1

Dipole Moments of Various Ketones
Benzene Solution, 25°C

	Compound	Moment (D)
(1)	Cholestane-3-one	3.01[12]
(2)	Androstane-17-one	2.98
(3)	Androstane-3,17-dione	2.94[13]
(4)	4,4-Dimethylcholestane-3-one[14]	2.78
(5)	4,4-Dimethyl-19-nor-androstane-3,17-dione[10]	2.68
(6)	4,4-Dimethyl-androstane-3,17-dione[11]	2.28
(7)	19-nor-Androstane-3,17-dione	2.90

[10] A. Bowers and H.J. Ringold, J.Amer.Chem.Soc. 81, 424 (1959).

[11] H.J. Ringold and G. Rosenkranz, J.Org.Chem. 22, 602 (1957).

[12] N.L. Allinger, M.A. DaRooge, H. Blatter and L. Freiberg, J.Org.Chem. 26, 2550 (1961).

[13] H.R. Nace and R.B. Turner, J.Amer.Chem.Soc. 75, 4063 (1953) report a dipole moment of 3.1 D for this compound. Since they did not account for atomic polarization in calculating the moment their value is slightly higher than ours.

[14] C. Djerassi, O. Halpern, V. Halpern and B. Riniker, J.Amer.Chem.Soc. 80, 4001 (1958).

The moments of (1) and (2) give the group moments of (3). A calculated value for the resultant moment of the latter was arrived at by projecting a Dreiding model of the molecule into a co-ordinate system, and determining the angle between the carbonyl groups and the resultant moment by standard trigonometric methods. It is estimated that the angle between the dipoles could be determined on the models to within 2 or 3° which gave errors of 0.1-0.2 D in the calculated moments. The moment calculated for (3) was 2.80 D, and the experimental value is 2.94 D, hence the model seems to portray the system to within the accuracy of measurement. As a check, the moment of (7) was determined and found to be 2.90 D, within experimental error of the value found for (3).

The presence of a 4,4-dimethyl grouping lowers the moment of the 3-ketone somewhat (from 3.01 in (1) to 2.78 in (4)). Using the group moments from (2) and (4), the moment of (5) was calculated, assuming a chair form. This assumption seems justified since there is no 1,3-diaxial dimethyl interaction. Here the calculated (2.75 D) and the experimental (2.68 D) values are in good agreement.

Table 2

Dipole Angles and Moments (D) for Possible Structures of (6)

Structure	Angle°	$\mu_{calc.}$ (D)
II	124	2.75
III	110	3.29
IV	121	2.88
V	131	2.46

Compound (6) was then examined. The angle between the dipoles of the ordinary chair was as for (3) and (5), 124° (Table 2). For boat IV this

angle was measured as slightly smaller (121°), while III has an angle of only 110°. These are the extremes of the flexible form, any angle between these limits is possible. The calculated moment of any boat form then is higher than that of II. The experimentally determined moment of (6) was, however, only 2.28 D, much smaller than calculated for the chair, and well outside of the range defined by the flexible form. A structure similar to the form V appears to be the only arrangement which will lower the calculated resultant moment. The value calculated for planar structure is 2.46 D, within experimental error of the measured value.

The rotatory dispersion curves[14] of 19-nordihydrotestosterone and its 4,4-dimethyl derivative show that the introduction of the latter grouping causes the predicted[1,15] large negative shift in the Cotton effect. The corresponding shift with the cholestan-3-one derivatives is similar though smaller, and is consistent with II. If III were the structure of these systems, a large positive shift would be predicted,[15] and its absence serves to eliminate this structure, but further conclusions do not appear warranted.

The planar form V should have the angle between C-2 and C-4 expanded slightly above its normal value. Such bond angle expansion has been detected[16] by the shift in carbonyl frequency using the relationship suggested by Halford[17]. The carbonyl frequencies of (1), (4) and of 4,4-dimethyl-19-norandrostan-17β-ol-3-one were therefore measured in chloroform solution. The latter showed absorption at 1706 cm^{-1}, as did (1). Compound (4) showed the predicted decrease to 1699 cm^{-1}.

The infra-red spectrum of (6) was determined, both in carbon tetrachloride

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15 C. Djerassi, Optical Rotatory Dispersion p.178. McGraw-Hill, New York (1960).

16 N.L. Allinger and S. Greenberg, J.Amer.Chem.Soc. 81, 5733 (1959).

17 J.O. Halford, J.Chem.Phys. 24, 830 (1956).

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solution, and as a mull. No bands could be detected in solution which were not present in the solid, although there was some change in the relative intensities of a few bands. With such a complicated molecule such a result may not be definitive, but it suggests the molecule is in a single conformation.

The structure of ring A in (6) which best fits the data is neither a chair nor a boat, but rather a flattened form in between the two.

Lehn, Levisalles and Ourisson[18] have preferred to interpret their data on a similar (but different) system as indicating an equilibrium between boat and chair forms. It may well be that their system behaves differently from the one studied by us. With our system we have found no evidence requiring a boat form, although the possibility of the presence of a small amount cannot be eliminated with certainty.

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[18] J. Lehn, J. Levisalles and G. Ourisson, following communication. We are indebted to Professor Ourisson for a copy of the manuscript prior to publication.

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CONFORMATION DU CYCLE A DE CÉTONES TRITERPÉNIQUES

ETUDE DE MOMENTS DIPÔLAIRES

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(Received 3 October 1961)

NOUS avons mesuré les moments dipôlaires[1] des dérivés triterpéniques suivants:

lupane (I):	$\mu = 0 \pm 0,02$ D[2]
lupanone (II):	$\mu = 2,99 \pm 0,03$ D[3]
nitrile de l'acide lupane carboxylique (III):	$\mu = 3,77 \pm 0,03$ D[4]
nitrile de l'acide lupanone carboxylique (IV):	$\mu = 3,93 \pm 0,03$ D[5]

Les deux dipôles présents dans le céto-nitrile sont éloignés d'environ 10 Å et ne peuvent avoir aucune action appréciable l'un sur l'autre. La conformation du cycle A dans les composés (II) et (IV) est par conséquent certainement identique. Il est donc possible de calculer le moment théorique du céto-nitrile (IV) par composition vectorielle des moments de groupes, pour une conformation donnée postulée, du cycle A, qui est le seul à

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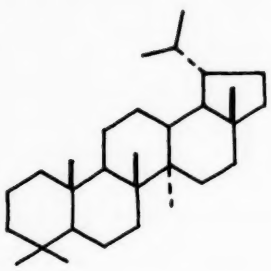
[1] Moments mesurés dans le benzène à 25°C, avec un Dipolmeter DM01 WTM; les mesures d'indice ont été faites avec un interféromètre de Raleigh.

[2] O. Heger, M. Montavon, R. Nowak et L. Ruzicka, Helv.Chim.Acta 30, 1869 (1947).

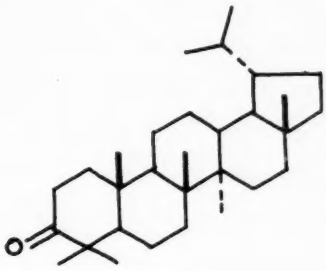
[3] I.M. Heilbron, T. Kennedy et F.S. Spring, J.Chem.Soc. 329 (1938).

[4] F = 270°5 - 271°5; $[\alpha]_D$ = - 8,2° ($CHCl_3$).

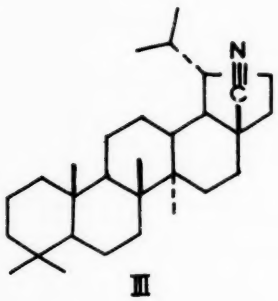
[5] F = 244° - 245°; $[\alpha]_D$ = + 18° ($CHCl_3$).



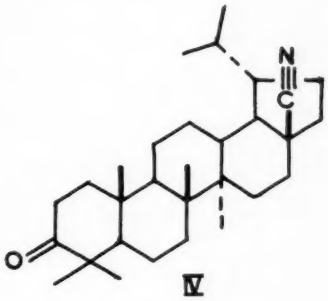
I



II



III



IV

présenter une mobilité conformationnelle.[6]

Les données géométriques nécessaires pour cette composition ont été mesurées sur des modèles moléculaires de Dreiding, auxquels nous avons dans tous les cas imposé une déformation du cycle B: les deux groupes méthyles axiaux en C-8 et C-10 ont été maintenus à 8,5 cm (soit 3,4 Å, leur distance de contact de Braude[7]).

La conformation classique chaise du cycle A, C, doit en outre etre déformée pour maintenir à 3,4 Å les groupes méthyles axiaux en C-4 et en

[6] H.R. Nace et R.B. Turner J.Amer.Chem.Soc. 75, 4063 (1953).

[7] E.A. Braude et F. Sondheimer, J.Chem.Soc. 3754 (1955).

C-10. Dans cette forme, l'angle des dipoles CN et CO est de 135°,[8] et le moment dipôlaire calculé résultant est 2,75 D.

Sur les modèles, cette conformation est d'ailleurs peu stable, et tend à passer spontanément dans l'une des conformations bateau.

La conformation bateau du cycle A, est ici très peu probable: elle conduirait à rendre maximum plusieurs interactions entre atomes non-liés. En particulier, les groupes méthyles en C-4 éclipseraient le groupe méthylene en C-6 et l'hydrogenène 5α. Une conformation plus vraisemblable en dérive, sans tension angulaire appréciable, par rotation vers une forme croisée, de façon à décaler d'environ 25° les liasons de C-4 et de C-5; les groupes méthyles β en C-4 et en C-10 restent ainsi à 3,4 Å l'un de l'autre. Cette forme "bateau déformé", D, conduit à un angle de 51° entre les dipoles CN et CO, et à un moment calculé de 6,1 D.

Enfin, nous avons également considéré la conformation intermédiaire "plane" P, du cycle A, proposée par Allinger et DaRooge dans la note précédente.[9] Cette conformation, où le carbonyle est coplanaire avec C_1, C_2, C_3, C_4 et C_5, conduit ici à un angle de 97° entre les dipôles composants, et à un moment calculé de 4,5 D.

Il est évidemment possible de faire intervenir pour le cycle A une conformation unique, déduite a posteriori du moment observé. On trouve alors que les dipôles CN et CO devraient être dirigés à 111° l'un de l'autre. Cet angle pourrait être réalisé de deux façons:

- soit à partir de la forme chaise C, en diminuant arbitrairement les déformations imposées, par example en rapprochant les méthyles axiaux dans le cycle B; cette hypothése nous semble

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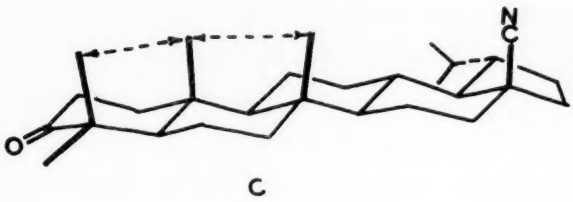
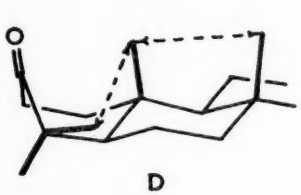
[8] Angles évalués à ± 1-2° donnant des erreurs de 0,1 à 0,2 D sur les moments calculés.

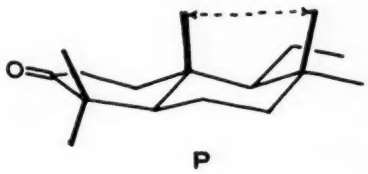
[9] N.L. Allinger et M.A. DaRooge: communication précédente.



C



D



P

Moments du Ceto-nitrile (III)

μ exp.	μ calc.		
	C	D	P
3,93 ± 0,03 D	2,75 ± 0,2 D	6,1 ± 0,2 D	4,5 ± 0,2 D

physiquement peu vraisemblable.[10]

- soit a partir de la forme "plane" P, en abaissant de 13° environ le carbonyle vers la face α. On aurait alors une forme chaise très déformée.

Bien que pour l'instant, nous ne puissons exclure objectivement l'hypothese d'une fixité conformationnelle, nous interprétons nos résultats en postulant un équilibre entre formes chaise C, et bateau déformé D contenant environ 70% de forme C et 30% de forme D.

Dans le cadre de cette hypothèse, les résultats d'Allinger et DaRooge[9] nous semblent aussi bien compatibles avec l'existence du cycle A sous forme

[10] Cf. les analyses roentgenographiques de composés 1,3-diméthylés, citées dans: R. Hanna, J. Levisalles et G. Ourisson, Bull.Soc.Chim. 1938 (1960).

chaise déformée C quasi-exclusive.[11]

Nous avons précédemment[10] postulé, pour expliquer leur dispersion rotatoire, que les 3-céto stéroides 4,4-diméthylés existaient sous forme chaise prépondérante, tandis que les 3-céto triterpènes, 8β-méthylés, existaient surtout sous forme bateau (nous dirions maintenant plutot; on grande partie...). Les mêmes données ont conduit Holker et Whalley[12] à des conclusions diamétralement opposées. Ces deux hypothèses, et celle d'une forme unique intermédiaire, sont évidemment contradictoires. On peut espérer que les travaux actuellement en cours dans plusieurs laboratoires, dont le notre, permettront un choix définitif et convaincant.

Nous remercions MM. Allinger et Whalley de nous avoir communiqué à l'avance le texte de leurs publications.

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[11] L'angle de 124° entre les deux dipôles C=O de la 4,4-diméthyl androstane-3,17-dione sous forme chaise non déformé est amené à 129° si l'on impose une distance de 3,4 Å entre les méthyles angulaires en C-4 et en C-10 (μ calc. 2,5 D). L'angle de 125°, qui est nécessaire pour retrouver numeriquement les résultats d'Allinger et DeRooge (μ exp. 2,28 D), est alors facile à obtenir par une petite déformation supplémentaire d'environ 6°; la conformation obtenue reste une chaise déformée.

[12] J.S.E. Holker et W.B. Whalley, sous presse.

Tetrahedron Letters No. 19, pp. 687-690, 1961. Pergamon Press Ltd. Printed in Great Britain.

SECONDARY DEUTERIUM ISOTOPE EFFECT ON THE MALEIC ANHYDRIDE-CYCLOPENTADIENE REACTION

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(Received 3 October 1961)

IT was demonstrated by Streitwieser et al.[1] that cyclopentyl tosylate-1-d is solvolyzed at 1/1.15 the rate of the protium analogue at 60°. The rate depression was ascribed to the change in bending frequency of the hydrogen (or deuterium) in proceeding from sp^3 hybridization in the reactant to nearly sp^2 in the transition state. Recently, Seltzer[2] has reported an inverse isotope effect where the hybridization change is from sp^2 in the reactant toward a partial sp^3 in the transition state. Maleic acid-2,3-d_2 was found to be converted to fumaric acid-2,3-d_2 at 1.17 times the rate of the protium analogue when catalyzed by thiocyanate ion at 60°.

We would like to report a small, inverse isotope effect in a common Diels-Alder reaction. Maleic anhydride-d_2 was synthesized by a procedure essentially identical to that of Seltzer's[2,3]. Mass spectral evidence indicated that the composition was 89.6% d_2, 7.7% d_1, and 2.7% d_0 corres-

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[1] A. Streitwieser, Jr., R.H. Jagow, R.C. Fahey and S. Suzuki, J.Amer. Chem.Soc. 80, 2326 (1858).

[2] S. Seltzer, J.Amer.Chem.Soc. 83, 1861 (1961); Chem. & Ind. 1313 (1959).

[3] A preprint of Dr. Seltzer's article was graciously sent prior to publication.

ponding to an atom fraction deuterium of 0.934. Combustion analysis[4] of an aliquot from a mixture of 4.995 g of the deuterated maleic anhydride and 4.928 g of normal isotopic species showed the atom fraction deuterium to be 0.4659 and 0.4668 in duplicate runs. This corresponds to an atom fraction deuterium of 0.9356 in the synthesized material.

The mixed maleic anhydrides were made up to 50.00 ml with methylene chloride, four 1/10 aliquots were brought to 0°, and reacted with cyclopentadiene sufficient to form adduct with 40% to 70% of the maleic anhydride. The cyclopentadiene was purified by passage through a Beckman GC-2 gas phase chromatography apparatus, calibrated by the recorder chart peak area, and passed directly into the reaction mixture. Reaction was assumed to be quantitative.[5]

The adduct (cis-3, 6-endo-methylene-1,2,3,6-tetrahydrophthalic anhydride) was isolated by removal of the residual maleic anhydride with fractional sublimation at 50°, and recrystallization of the product from toluene followed by sublimation at 100°. The melting points of the samples submitted for combustion analysis ranged from 158 to 162°. This product has been shown to have the endo configuration and to be formed by kinetic control.[6,7]

Calculation of the k_D/k_H ratio was done by substituting appropriate quantities in the equation[8]

$$k_D/k_H = \frac{\log a_D/a_D^\circ}{\log a_H/a_H^\circ} \qquad (1)$$

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[4] Deuterium analyses were by Josef Nemeth, Urbana, Ill.

[5] O. Diels and K. Alder, Liebigs Ann. 460, 98 (1928).

[6] D. Craig, J.Amer.Chem.Soc. 73, 4889 (1951).

[7] J.A. Berson, R.D. Reynolds and W.M. Jones, J.Amer.Chem.Soc. 78, 6049 (1956).

[8] L. Melander, Isotope Effects on Reaction Rates p. 49. The Ronald Press Co., New York (1960).

Since the amount of maleic anhydride-d_1 is small and the k_D/k_H ratio is close to unity, the ratio of adduct-d_1 to adduct-d_2 was assumed to be the same as the maleic anhydride-d_1-maleic anhydride-d_2 ratio in the starting mixture. The table below summarizes the results:

Wt. cyclopentadiene (g)	Moles cyclopentadiene / Moles maleic anhydride	Atom fraction deuterium in adduct[4]	k_D/k_H
0.259	0.391	0.1189	1.05
0.336	0.507	0.1196	1.07
0.387	0.584	0.1188	1.05
0.451	0.681	0.1185	1.06
		Average:	1.06

It is clear that a small, but real, inverse isotope effect is present in the reaction. Using a simplified equation derived by Streitwieser,[1]

$$k_D/k_H = e^{-0.187/T\sum_i(\nu_{Hi} - \nu^{\ddagger}_{Hi})} \qquad (2)$$

and taking only the change in the out-of-plane bending motion as significant (769 cm^{-1} to 1340 cm^{-1}), one finds the maximum isotope effect to be 2.2 for the simultaneous conversion of two sp^2 carbon atoms to sp^3; the expected maximum for a single carbon atom hybridization change is 1.5. From the temperature dependence of the isotope effect, Seltzer[2] has estimated that his rate enhancement of 15% corresponds to a transition state approximately one-half way between sp^2 and sp^3 (for one carbon atom). Whether the rate-determining step of the Diels-Alder reaction involves one[9] carbon atom of the dienophile or both,[10] the hybridization change at the transition state for the maleic anhydride-cyclopentadiene case is seen to be small.

[9] R.B. Woodward and T.J. Katz, Tetrahedron 5, 70 (1959); Tetrahedron Letters No. 5, 19 (1959).

[10] M.J.S. Dewar, Tetrahedron Letters No. 4, 16 (1959).

Acknowledgment - This work was supported by Stanford Research Institute through funds administered by the Physical and Biological Sciences Division Research Committee.

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Tetrahedron Letters No. 19, pp. 691-695, 1961. Pergamon Press Ltd. Printed in Great Britain.

THE DISPROPORTIONATION OF ETHYLBENZENE-1-C_1^{14} UNDER THE INFLUENCE OF ALUMINUM BROMIDE AND HYDROGEN BROMIDE[1]

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(Received 29 September 1961)

It is known[3] that the disproportionation[4] of ethylbenzene to give benzene and a mixture of di- and triethylbenzenes catalyzed by hydrogen bromide promoted aluminum bromide is much faster than the corresponding disproportionation of toluene. McCaulay and Lien[3] have explained the huge rate difference on the basis of hyperconjugative stabilization of the transition state in the case of ethylbenzene. Brown and Smoot[5] modified this mechanism by suggesting that the first formed sigma complex rapidly isomerized to a π-complex, which complex was in mobile equilibrium with the starting material. Thus according to this concept, the rate determining step involving two molecules of alkyl benzene depends on the concentration of this π-complex which could reasonably be expected to be significantly higher than the corresponding π-complex derived from toluene.

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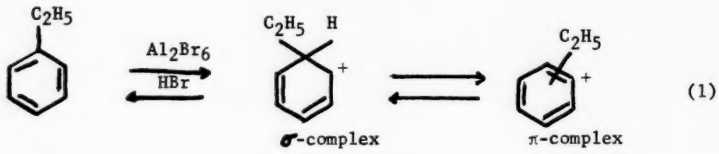
[1] Research performed under the auspices of the U.S. Atomic Energy Commission.

[2] International Cooperation Administration Fellow, Brookhaven National Laboratory, 1958-1959.

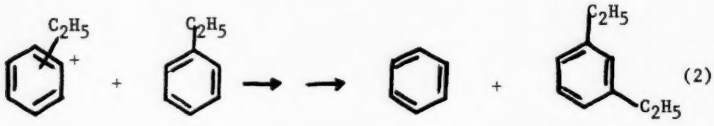
[3] D. A. McCaulay and A. P. Lien, J. Amer. Chem. Soc. 75, 2411 (1953).

[4] This term means primarily transalkylation but actually embraces intramolecular isomerization and isomerization resulting from intermolecular reactions, all of which are occurring at varying rates under the usual reaction conditions for "disproportionation."

[5] H. C. Brown and C. R. Smoot, J. Amer. Chem. Soc. 78, 2176 (1956)



(1)



(2)

Streitwieser and Reif[6] have suggested another mechanism involving oxidation to the α-phenethyl cation as being operative. Recent work by Douglass and Roberts[7] and by Nenitzescu et al.[8] also bears on this problem.

In an effort to provide more detailed information on the disproportionation reaction we studied the reaction using ethylbenzene-1-C_1^{14}. The use of one-labeled material bears on the existence of a π-complex as a transitory intermediate and on the relation of isomerization to transalkylation. Ethylbenzene-1-C_1^{14} was prepared from commercially available benzoic acid-1-C_1^{14}. The acid was reduced to benzyl alcohol from which benzyl chloride was prepared. Treatment of this material with dimethyl sulfate gave ethylbenzene-1-C_1^{14} in 60 % overall yield.

The reaction was carried out without solvent under conditions similar to those of Brown and Smoot.[5] The reaction was quenched after a contact time of about seventeen minutes. Use was made of the degradation scheme of J. D. Roberts et al. Adipic acid was also prepared from the cyclohexanone

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[6] A. Streitwieser Jr. and L. Reif, J. Amer. Chem. Soc. 82, 5003 (1960).

[7] J. E. Douglass and R. M. Roberts, Chem. and Ind. 926 (1959).

[8] C. D. Nenitzescu, I. Necsoiu, A. Glatz and M. Zalman, Chem. Ber. 92, 10 (1959).

[9] J. D. Roberts, D. A. Semenow, H. E. Simmons, Jr. and L. A. Carlsmith, J. Amer. Chem. Soc. 78, 601 (1956).

intermediate and this was degraded via Schmidt reactions. In addition glutaric acid was prepared via cyclopentanone prepared from the adipic acid. Glutaric acid and δ-aminovaleric acid were prepared from the cyclopentanone. These acids were also degraded via Schmidt reactions. The results of the degradations are given in Table I.

Calculations using the CO_2 value for the one position and using the diamine values in simultaneous equations gave the specific activities for each position. These are listed in Table II. Larger errors are involved if the CO_2 values alone are used. Both methods involve considerable error since one is dealing with small differences in large numbers. Ring distribution is shown in Fig. 1.

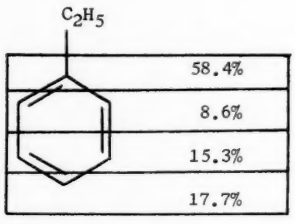

Fig. 1. Activity distribution in recovered ethylbenzene

Clearly rearrangement with respect to the specifically labeled position has taken place. It is further evident that the bulk of the rearranged activity is now in the meta and para positions (the errors involved notwithstanding). This consequence unequivocally eliminates a localized π-complex as a major intermediate which is involved in a prior equilibrium in this reaction (cf. equations 1 and 2).

The fact that the specific activity of the ortho position is lower than that specific activity of the para position clearly shows that trans-

Table I. Summary of Activities in Various Positions

Compound[a] Assayed	Source of Activity Relative to Position in Benzene Ring	Value
1. benzoic acid	all positions	0.156 mμc/mgC
2. CO_2; ε-aminocaproic acid	100% #1	0.625 mμc/mgC
3. CO_2; adipic acid	0.5 #1; 0.5 o	0.342 mμc/mgC
4. CO_2; δ-aminovaleric acid	0.5 #1; 0.5 o	0.330 mμc/mgC
5. CO_2; glutaric acid	0.25 #1; 0.5 o; 0.25 m	0.192 mμc/mgC
6. 1,5-pentamethylenediamine	0.4 o; 0.4 m; 0.2 p	0.0891 mμc/mgC
7. 1,4-pentamethylenediamine	0.25 o; 0.5 m; 0.25 p	0.100 mμc/mgC
8. 1,3-trimethylenediamine	0.166 o; 0.5 m; 0.333 p	0.112 mμc/mgC

[a] Control degradations on unreacted starting material indicated at least 98% of the activity to be in the one position.

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alkylation (or intermolecular migration of an ethyl group) must occur more rapidly than a succession of 1-2 intramolecular ethyl group shifts.[10] These results would tend to support the view that rapid transalkylation to give p-diethylbenzene occurs, which compound then can isomerize and/or transalkylate further. Studies to determine the relative rates of transalkylation and isomerization of the ethylbenzenes are in progress in this laboratory.

Table II. Specific Activities for Each Ring Position

Position	Source	Value	Error
#1	CO_2	0.625 mμc/mgC	± 4%
ortho	diamine	0.046 mμc/mgC	±42%
meta	diamine	0.082 mμc/mgC	±45%
para	diamine	0.190 mμc/mgC	±45%
ortho	CO_2	0.048 mμc/mgC	±27%

[10] Bridged intermediates or transition states involving 1,3 or 1,4 shifts will not be considered in this short communication.

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Tetrahedron Letters No. 20, pp. 697-701, 1961. Pergamon Press Ltd. Printed in Great Britain.

SUBSTANCES FROM PETASITES OFFICINALIS MOENCH. AND PETASITES ALBUS (L.) GAERTN.

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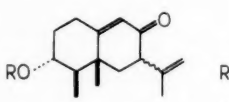
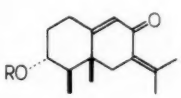
(Received 30 October 1961)

DURING recent years, Stoll and co-workers[1] and Aebi, Büchi and Waaler[2-5] investigated substances from coltsfoot rhizomes mainly in connection with their studies concerning spasmolytically active compounds. They isolated new types of substances as e.g. petasin (I), isopetasin (II) and S-petasin (III). The constitution of these interesting substances which are further representatives of sesquiterpenic compounds belonging to eremophilane type, has been elucidated by the authors named at last.[2-5]





I R = $COC(CH_3)=CHCH_3$ II R = $COC(CH_3)=CHCH_3$

III R = $COCH=CHSCH_3$

[1] A. Stoll, R. Morf. A. Rheiner and J. Renz, Experimentia 12, 360 (1956). cf. also: A. Stoll, J. Renz and R. Morf, Referatenband XIV. Internationaler Kongress für reine und angewandte Chemie Referat 306. Zürich (1955).

[2] A. Aebi, J. Büchi, T. Waaler, E. Eichenberger and J. Smutz, Pharm. Acta Helv. 30, 277 (1955).

[3] A. Aebi, T. Waaler and J. Büchi, Pharm. Weekblad 93, 397 (1958).

[4] T. Waaler, Dissertation, ETH Zurich (Prom. Nr. 2658) Juris Verlag (1958).

[5] A. Aebi and T. Waaler, Über die Inhaltstoffe von Petasites hybridus (L.) Fl. West. Verlag Helbing und Lichtenbahn, Basel (1959).

The absolute configuration of petasin has been ascertained by Aebi and Djerassi[6] on the basis of rotatory dispersion measurements and by Herbst and Djerassi[7] on the basis of proofs provided by synthesis. The configuration on carbon atom substituted with isopropylene group remained, however, uncertain.

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As a part of an extensive study of sesquiterpenic lactones from Compositae, we had been concerned, at the time the papers mentioned were published, in isolation and structure of compounds from Petasites officinalis Moench,, syn. P. hybridus (L.) Fl. Weet. and further from Petasites albus (L.) Gaertn. Chromatography of rhizomes extracts and subsequent crystallisation of particular eluates afforded a series of new compounds, different from those hitherto reported.[1-5] This Communication summarizes our results; it is hoped to publish this work in full detail in a series of papers in Coll. Czech. Chem. Comm.

The substances isolated, the physical constants of which are outlined in Table 1, fall essentially into two parts: substances of furane type [furanoeremophilane (IV), furanoeremophilone (V), petasalbin (VI), albopetasin (VII), albopetasol (VIII) and furanopetasin (IX)] and compounds containing α,β-unsaturated δ-lactonic grouping [eremophylenolide (X), petasitolide A (XI), petasitolid B (XII) and S-petasitolide A (XIII) and B (XIV)]. In both plants, we succeeded to find also the sesquiterpenic hydrocarbon eremophilen (XV) which contains one methylene double bond and one trisubstituted ethylenic linkage. Tentative formulae suggested for compounds IV-VII and IX-XIV may be seen in Fig. 1.

The structures were elucidated especially on the basis of conversion of all mentioned oxygen-containing compounds into the same 8,12-oxidoeremo-

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[6] A. Aebi and C. Djerassi, Helv. Chim. Acta 42, 1785 (1959).

[7] D. Herbst and C. Djerassi, J. Amer. Chem. Soc. 82, 4337 (1960).

philane (XVI). On hydrogenation and on hydrogenolysis, some compounds (eremophilene, furanoeremophilane, eremophilenolide and petasalbin) afforded even the hydrocarbon eremophilane (XVII) which for comparison purposes was prepared from hydroxydihydroeremophilone.*

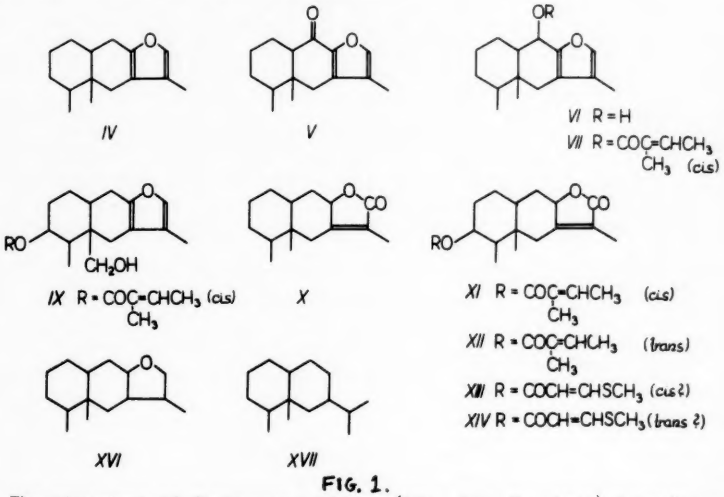

FIG. 1.

The structure of furanoeremophilane (IV; from P. albus) formulae see (Fig. 1) which besides double bonds in the furane ring contains no other ethylenic linkage, followed from the identification of its hydrogenation product. Furanoeremophilone (V; from P. officinalis) has its ketonic carbonyl conjugated with furane ring and its structure ensued from conversion into a derivative, identical with a product of petasalbin reduction. Petasalbin (VI; from P. albus) contains, besides a furane ring, a secondary hydroxyl group in allylic position and structure VI has been allotted to it. Albopetasin (VII; from P. albus) is an angelate ester of petasalbin. Albopetasol (VIII; from P. albus) contains a furane ring and two hydroxyl groups, the location of which is still uncertain. Furanopetasin (IX; from P. officinalis) contains a primary and a secondary hydroxyl group, the latter

* We are greatly indebted to Dr. M.D. Sutherland, University of Brisbane, Australia, for a sample of hydroxydihydroeremophilone.

Table 1

Compound	Formula	m.p.	$[\alpha]_D^{20}$	Characteristic bands in the spectrum	
				Infra-red (cm^{-1})	Ultra-violet
Furanoeremophilane IV	$C_{15}H_{22}O$	*	- 8.4°	1576,1660, 1776,1810	222 mμ; log ε 3,779
Furanoeremophilone V	$C_{15}H_{20}O_2$	150°	± 0°	1537 3000, 1667	280 mμ; log ε 4,18
Petasalbin VI	$C_{15}H_{22}O_2$	81-82°	- 11.2°	1567,3485 3615	220 mμ; log ε 3,836
Albopetasin VII	$C_{20}H_{28}O_3$	106-7°	± 0°	1572,1653, 1718	224 mμ; log ε 4,075
Albopetasol VIII	$C_{15}H_{22}O_3$	178-80°	- 24.1°	1568,1652, 3320,3370	220 mμ; log ε 3,817
Furanopetasin IX	$C_{20}H_{28}O_4$	105-6°	± 0°	1567,1655,1718, 3450,3608	222 mμ; log ε 4,17
Eremophilenolide X	$C_{15}H_{22}O_2$	125°	+ 16.6°	1750,1760, 1699,1038	220-224 mμ; log ε 4,162
Petasitolide A XI	$C_{20}H_{28}O_4$	147°	+ 48°	1762,1712 1650	218 mμ; log ε 4,420
Petasitolide B XII	$C_{20}H_{28}O_4$	146°	+ 31.8°	1761,1713 1650	219 mμ; log ε 4,447
S-petasitolide A XIII	$C_{19}H_{26}O_4S$	201-2°	- 15.3°	1695,1572, 1750	219 mμ; log ε 4,339 288 mμ; log ε 4,223
S-petasitolide B XIV	$C_{19}H_{26}O_4S$	199-200°	- 32.9°	1695,1571, 1750	219 mμ; log ε 4,193 289 mμ; log ε 4,167
Eremophilene XV	$C_{15}H_{24}$	**	- 104.2°	885,1642, 1780,3085	

* B.p. 148°/16 mm, d_4^{20} 1,0270; n_D^{20} 1,5172.

** B.p. 132°/19 mm, d_4^{20} 0.9325; n_4^{20} 1,5067.

being esterified with angelic acid. The location of both hydroxyl groups follows, in sense of formula IX, from chemical and physical properties of the substance.[8]

Besides santanolides, alantanolides, guaianolides, the group of newly isolated eremophilenolides represents a further type of sesquiterpenic lactones from Compositae.

Eremophilenolide (X; from P. officinalis) which has the less complicated structure, was converted into eremphilone (XVIII, Fig. 1) by the method used earlier for conversion of santanolide "c" into dihydrojunenol;[9] the infra-red spectrum of XVIII exhibited band at 1430 cm^{-1} due to a methylene group adjacent to ketonic carbonyl (1711 cm^{-1}).

The group of petasitolides and S-petasitolides (XI-XIV); (from P. officinalis) is derived from hydroxyeremophilenolide XIX which is esterified with angelic acid (petasitolide A XI), tiglic acid (petasitolide B XII) and cis- or trans-β-methylthioacrylic acid (S-petasitolide A (XIII) or B (XIV).

[8] L. Novotný, Ch. Wlotzka, V. Herout and F. Šorm, Coll. Czech. Chem. Comm. In press.

[9] B.C. Bhattacharyya, A.S. Rao and A.M. Shaligram, Chem. & Ind. 469 (1960).

Tetrahedron Letters No. 20, pp. 702-706, 1961. Pergamon Press Ltd. Printed in Great Britain.

STRUCTURE OF VINCAMINE

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(Received 23 October 1961)

VINCAMINE (minorine), an alkaloid constituent of Vinca minor L.[1-10] Vinca erecta Rgl. et Schmalh.[11-13], and Vinca difformis Pourr.[14], has the molecular formula $C_{21}H_{26}N_2O_3$, in satisfactory agreement with the experimentally determined molecular weight[1,5]. The ultra-violet spectrum shows it to be an indole derivative. Further structural information was obtained from the infra-red spectrum in Nujol, with bands at 747, 727 (1,2-

1 E.S. Zabolotnaya, Trudy Vsesoyuznovo Nauchno-Issledovatelskovo Instituta Lekarstvěnych Rastenii (Moscow) No. 10, 29 (1950).

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5 F.E. King, J.H. Gilks and M.W. Partridge, J.Chem.Soc. 4206 (1955).

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10 P.N. Lyapunova, private communication.

11 P.Kh. Yuldashev, Izv.Akad.Nauk SSSR 188 (1953).

12 S.Yu. Yunusov, P.Kh. Yuldashev and N.V. Plechanova, Dokl.Akad.Nauk. Uz.S.S.R. 13 (1956).

13 S.Yu. Yunusov and P.Kh. Yuldashev, Zh.Obshch.Khim. 27, 2015 (1957).

14 M.M. Janot, J.Le Men and Ch. Fan, Ann.Pharm.Fr. 15, 513 (1957).

disubstituted benzene ring[14]), 1756 (saturated ester[2]) and 1074 cm^{-1} (C-OH[4]). The band at 3320 cm^{-1} (characteristic for the NH-grouping) was absent. The infra-red spectrum in chloroform solution showed an additional band of medium intensity at 3520 cm^{-1}, characteristic for the O-H group. The titration equivalent[6] and salt formation,[2] indicate that vincamine is a monoacid base; the basic nitrogen atom $N_{(b)}$ is tertiary, as shown by the formation of a monomethiodide, m.p. 218-220° (Found: C, 53.38; H, 6.10. $C_{22}H_{29}N_2O_3I$ requires: C, 53.23; H, 5.89.). Schlittler and Furlenmeier[2] reported that vincamine has one active hydrogen atom, no $N\text{-}CH_3$ or $C\text{-}CH_3$ grouping and cannot be acetylated with acetic anhydride in pyridine.

From our own experiments, we propose the formula Ia for vincamine. Vincamine (Ia) takes up no hydrogen in the presence of Adams' catalyst in methanol or in acetic acid. With potassium hydroxide in boiling methanol it affords vincaminic acid (Ib), m.p. 262-263° (Found: C, 70.56; H, 7.29. $C_{20}H_{24}N_2O_3$ requires: C, 70.56; H, 7.11.) (infra-red spectrum in Nujol: 1670 cm^{-1} - saturated carboxylic acid), which may be reconverted to the parent compound Ia by the action of diazomethane. On being heated to 220° or by reaction with acetic anhydride vincamine (Ia) loses one molecule of water forming apovincamine (II), m.p. 160-161° (Found: C, 74.64; H, 7.18. $C_{21}H_{24}N_2O_2$ requires: C. 74.97; H, 7.19.). The shift of the ester carbonyl band in the infra-red spectrum of II (in chloroform) to shorter frequencies (10 cm^{-1}) against Ia as well as the appearance of two new bands at 1618 and 1638 cm^{-1} suggests extended conjugation in II. The striking difference in the ultra-violet spectra of Ia and II (λ_{max} in mμ(log ε): 228 (4.45); 273 (4.04); 313 (3.82)) makes it probable that the newly formed double bond is conjugated with the indole nucleus. Dehydrogenation of Ia with lead tetra-acetate afforded py-tetradehydrovincamine chloride, m.p. 223-226° (Found: C, 64.31; H, 5.82. $C_{21}H_{23}N_2O_3Cl.1/4\ H_2O$ requires: C, 64.44; H, 6.05.)

as the main product; the ultra-violet spectrum of this compound, λ_{max} in mμ (log ε) : 255 (4.47); 308 (4.33); 370 (3.80), is practically identical with that of py-tetradehydroyohimbine chloride (λ_{max} in mμ (log ε) : 255 (4.47); 305 (4.31; 365 (3.65)). A byproduct of the dehydrogenation, not further characterized, showed an ultra-violet spectrum (λ_{max} in mμ (log ε) : 250 (4.06); 357 (4.14)), typical for a 3-dehydro-β-carboline. The β-carboline structure of Ia is also confirmed by the displacement of the ultra-violet absorption maxima of Ia to shorter wavelengths in acidic solution as against neutral or alkaline solution. This shift, characteristic for the protonation or quarternization of alkaloids of the β-carboline type on $N_{(b)}$,[15] was observed not only for Ia but also for Ia-methiodide and Ib.

Acid hydrolysis of Ia gave amphoteric products together with a base, m.p. 174°, (Found: C, 77.47; H, 7.72. $C_{19}H_{22}N_2O$ requires: C, 77.52; H, 7.53.), which was shown to be identical by both ultra-violet and infra-red spectra with eburnamonine (III),[16] an alkaloid of Hunteria eburnea Pichon[17-19]. The elemental formulae of vincamine (Ia) and eburnamonine (III) differ by $C_2H_4O_2$; of this CH_2 is evidently attributable to the methyl ester group of Ia leaving the elements of formic acid to be accounted for. The loss of these fragments on acid hydrolysis is best interpreted by primary hydrolysis of the methyl ester Ia to the acid Ib, followed by elimination of the elements of formic acid, behaviour typical of a α-hydroxyacid. These

[15] W. Arnold, W.v. Philipsborn, H. Schmid and P. Karrer, Helv.Chim.Acta 40, 708 (1957).

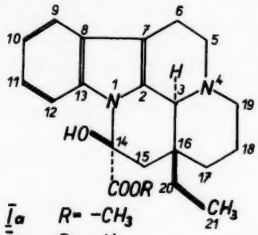
[16] Physical Data of Indole and Dihydroindole Alkaloids (4th. Ed.) Eli Lilly (1960).

[17] M.F. Bartlett, W.I. Taylor and Raymond-Hamet, C.R.Acad.Sci.,Paris 249, 1259 (1959).

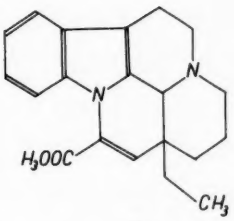
[18] M.F. Bartlett and W.I. Taylor, Tetrahedron Letters No. 20, 20 (1959).

[19] M.F. Bartlett and W.I. Taylor, J.Amer.Chem.Soc. 82, 5941 (1960).

considerations lead to the formula Ia for vincamine.



Ia R= $-CH_3$
Ib R= -H



II

Further evidence for structure Ia was obtained from the chromic acid oxidation of Ia by the method of Garbers, Schmid and Karrer[20]. Unlike Schlittler and Furlenmeier[2], who were not able to establish the presence of C-methyl grouping, we have found both acetic and propionic acid among the oxidation products of Ia, proving the presence of a C-ethyl group.

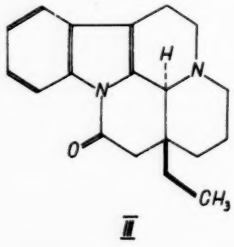
The above transformations also give stereochemical information about all three centres of asymmetry in vincamine (Ia), at $C_{(3)}$, $C_{(14)}$ and $C_{(16)}$. The trans-annelation of rings D and E, i.e. the relative configuration at $C_{(3)}$ and $C_{(16)}$, follows from the transformation of Ia to III, the stereochemistry of the latter already being well established.[19] The configuration of the remaining asymmetric centre at $C_{(14)}$ follows from the ready dehydration of vincamine (Ia) to apovincamine (II) under conditions characteristic for bimolecular trans-elimination. For a rigid structure such as Ia this requires the hydroxyl group to be cis to the ethyl group on $C_{(16)}$ and axial in conformation; the relatively bulky methoxycarbonyl group would then have the thermodynamically favoured equatorial orientation. The relative stereochemistry of vincamine is indicated in formula Ia..

Interesting conclusions may be drawn about the absolute configuration of Ia. Bartlett, Taylor and Raymond-Hamet[17] consider eburnamonine (III)

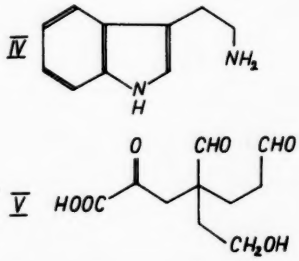
[20] C.F. Garbers, H. Schmid and P. Karrer, Helv.Chim.Acta 37, 1336 (1957).

to have the same configuration of the ethyl group as aspidospermine and hence deduce the absolute configuration at $C_{(3)}$ and $C_{(16)}$ of III. Whereas native eburnamonine from Hunteria eburnea has $[\alpha]_D = +89^\circ$ (in chloroform)[17], the degradation product of vincamine (Ia) had a rotation of approximately the same value but of opposite sign ($[\alpha]_D = -105^\circ$ (c = 0.44, in chloroform)). Vincamine (Ia) thus evidently represents an antipode of the alkaloids of Hunteria eburnea. This finding affords a further example for existence in nature of antipodes with identical fundamental structures in addition to the known pairs (+) and (-) quebrachamine,[21] (+) and (-) akuammicine,[22] and pyrifolidine-aspidospermine.[23]

Structure Ia is also in full accord with biogenetic requirements. As in the biogenesis of eburnamonine (III),[24] tryptamine (IV) and diformyl-hydroxyketokarboxylic acid (V) are the most likely precursors. Closure of ring E may be interpreted as an addition of the indole nitrogen to the keto group giving rise to the rather unusual α-hydroxy-α-aminoacid grouping hitherto found only in the peptide moiety of the ergot alkaloids.



II



The authors express their appreciation to Mr. M. Filip for the micro-analyses.

21 T.H. Henry, The Plant Alkaloids (4th. Ed.) p.511 (1949); F. Walls, O. Collers and A. Sandoval, Tetrahedron 2, 173 (1958).

22 P.N. Edwards and G.F. Smith, Proc.Chem.Soc. 215 (1960).

23 C. Djerassi, B. Gilbert, J.N. Shoolery, L.F. Johnson and K. Biemann, Experientia 17, 162 (1961).

24 H.G. Boit, Ergebnisse der Alkaloid-Chemie bis 1960 p.642 (1961).

Tetrahedron Letters No. 20, pp. 707-715, 1961. Pergamon Press Ltd. Printed in Great Britain

THE STRUCTURE OF TUBEROSTEMONINE

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(Received 21 August 1961; in revised form 25 October 1961)

Tuberostemonine, $C_{22}H_{33}NO_4$, constitutes the major alkaloid of Stemona tuberosa. H.Schild[1] described a number of degradation reactions on an alkaloid, $C_{22}H_{33}NO_4$, isolated from Stemona sessifolia. A group of Japanese workers[2] showed that Schild's alkaloid was identical with tuberostemonine isolated by K.Suzuki from Stemona tuberosa[3]. Subsequent studies led to the clarification of the funcional groups; tuberostemonine is a tertiary base[1], containing two γ-lactone rings[4].

Our own studies can be summarized by the structures Ia or Ib. Tuberostemonine melts at 86-88°, pK = 6.4 (60% ethanol), IR (KBr): ν_{max} 1765 cm^{-1}. The NMR spectrum[5] of the base reveals three C-methyl groups. Two sharp peaks at 8.63 and 8.77 ppm are either two unsplit C-methyls or two superimposed doublets. That the latter is the case will become obvious in

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[1] H.Schild, Ber. 69, 74 (1936).

[2] H.Kondo, K.Suzuki and M.Satomi, J.Pharm.Soc.Japan 59, 177 (1939).

[3] K.Suzuki, J.Pharm.Soc.Japan 54, 96 (1934).

[4] T.Kaneko, Ann.Rep. ITSUU Lab. 11, 45 (1960).

[5] All NMR spectra are measured in $CDCl_3$ with $(CH_3)_4Si$ as internal reference.

the sequel. Since both C-methyls are deshielded, they may be placed α to the lactone carbonyls. A third C-methyl group, split into a badly resolved triplet, is centered at 9.02 ppm. A multiplet at 5.62 ppm with the integrated area of two protons accounts for the two secondary γ-hydrogens of the lactones. The spectrum proves the absence of N-methyl; the Zeisel determination indicates the absence of N-alkyl. Experiments to demonstrate a CC double bond were negative. We can therefore conclude that tuberostemonine contains two hetero- and one carbocyclic ring, in addition to the γ-lactones.

Permanganate oxidation[1] of the alkaloid yields 1-methyl-succinic acid ($[\alpha]_D^{24^\circ} = -12.6^\circ$) and a neutral compound II, m.p. 135-138°. Found: C, 69.92; H, 8.95; O, 16.30; N, 4.77; C-CH_3, 9.4 . IR (KBr): ν_{max} 1765 cm^{-1} (γ-lactone), 1685 cm^{-1} (γ-lactam). The NMR spectrum exhibits a doublet for one C-methyl at 8.70 and a triplet at 9.03 ppm. The oxidative cleavage of I into 1-methyl-succinic acid and II leaves no doubt that the two C-methyls deshielded in tuberostemonine have to be placed at different carbons. The formation of optically active methylsuccinic acid proves, furthermore, that both deshielded C-methyls in I are doublets.

Tuberostemonine reacts with three moles of phenyl magnesium bromide to afford III, m.p. 178-187°. Found: C, 78.52; H, 8.27; O, 10.89; N, 2.48; C-CH_3, 6.26. IR (KBr): ν_{max} 1605(w) cm^{-1}.

On treatment of III with acetic acid/acetic anhydride at room temperature, a double bond is introduced by loss of

the elements of water and the secondary hydroxyl is acetylated to give IV, m.p. 85-93°. Found: C, 79.56; H, 8.45; O, 10.05; N, 2.05; C-CH_3, 8.8; O-Ac, 5.9. IR (KBr): ν_{max} 1735, 1600(w) cm^{-1}. UV (ethanol): λ_{max} 280 mμ, ε =9900. The NMR spectrum shows a multiplet for one proton at 4.81 ppm (α hydrogen of secondary acetate), and singlets at 7.85 ppm (acetate) and 8.1 ppm (methyl on a CC double bond). A multiplet at 8.81 - 9.13 ppm proves the presence of the two remaining C-methyls.

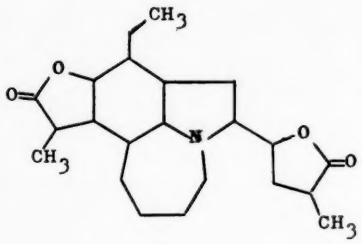
On oxidation of IV with CrO_3 in acetic acid a methyl ketone (V) is obtained. IR ($CHCl_3$): ν_{max} 3400, 1723 (sh., acetate), 1715 (ketone, benzoate), 1605(w) cm^{-1}. The NMR spectrum clarifies the functionality of V: two protons at 2.08 ppm represent the ortho hydrogens of the benzoate, 13 protons at 2.54 - 2.89 ppm are the rest of the aromatic hydrogens. The secondary hydrogen α to the benzoate, expected at 4.88, is deshielded by the methyl ketone in β-position to 4.54 ppm. A one proton multiplet at 4.91 ppm is in agreement with a secondary acetate, and singlets at 7.89 and 7.92 ppm account for the acetyl group and the methyl ketone, respectively. V cannot be recrystallized since it loses benzoic acid with extreme ease.

Passing of V through basic alumina yields on elution with benzene-ether an α,β-unsaturated methyl ketone (VIa or b), m.p. 105-120°. Found: C, 79.06; H, 8.71; O, 10.10; N, 2.19; C-CH_3, 6.99. IR ($CHCl_3$): ν_{max} 3600, 3400, 1670, 1620(w), 1610(w) cm^{-1}. UV (ethanol): λ_{max} 225 mμ, ε =12000. The NMR spectrum shows a doublet at 3.37 ppm for the β-hydrogen of

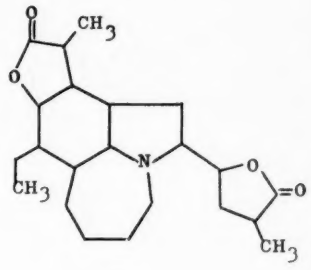
the unsaturated ketone, the methyl ketone peak appears at 7.69 ppm and the remaining two C-methyls are at 8.82 - 9.15 ppm (m).

Refluxing of VI in ethanol/KOH in the presence of air gives basic and acidic material. In addition to starting material, the chromatography of the basic fraction through basic alumina yields pale yellow crystals (VII), m.p. 185 - 189°. Found: C, 79.72; H, 7.70; O, 9.40; N, 2.38. IR ($CHCl_3$): ν_{max} 3600, 3400, 1680, 1605(m), 1570(m) cm^{-1}. UV (ethanol): λ_{max} 252 mμ, ε = 17800; λ_{max} (sh) 275 mμ, ε = 8700; λ_{max} 354 mμ, ε = 1900. UV (ethanol/HCl): λ_{max} 252 mμ, ε=12900; λ_{max} 282 mμ, ε = 3200. The UV spectrum in ethanol is typical for an ortho- or meta-amino acetophenone. The UV spectrum in acidic solution is characteristic for an alkyl-substituted acetophenone [6]. The NMR spectrum of VII exhibits eleven hydrogens in the aromatic region (2.49 - 2.77 ppm); the methyl ketone at 7.47 ppm is in excellent agreement with an acetophenone. A C-methyl triplet (J_{AB} = 6.6 cps) is centered at 8.82 ppm, the expected position for an ethyl benzene. The remaining C-methyl doublet appears again at 9.1 ppm. The UV spectrum does not differentiate between an ortho- or meta-amino acetophenone. However, the NMR spectrum clearly shows the presence of one hydrogen on the newly formed aromatic ring, and the substitution pattern could be decided by a study of the shifts of this hydrogen in approp-

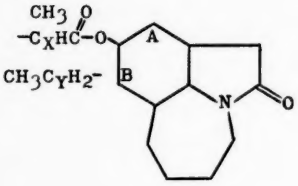
[6] E.A.Braude and F.Sondheimer, J.Chem.Soc. 1955 3754



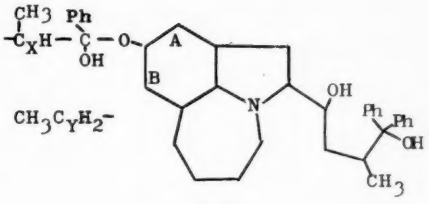
Ia



Ib

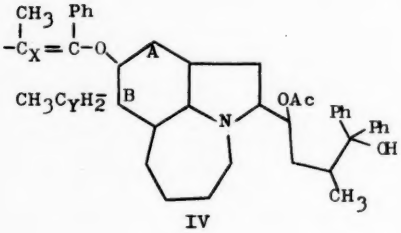


II

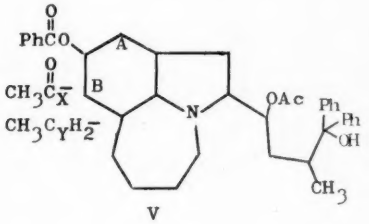


III

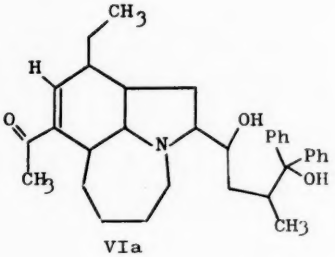
(C_X joined to C_A, C_Y to C_B, or vice versa)



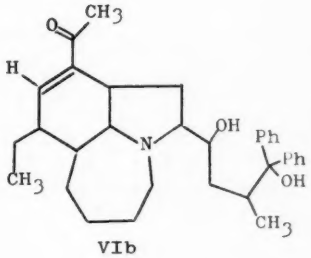
IV



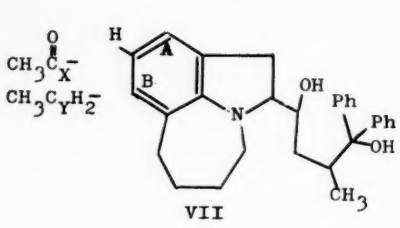
V



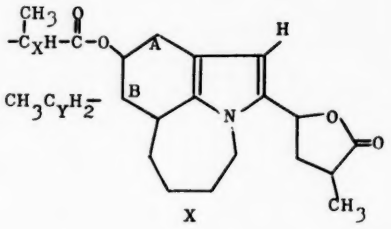
VIa



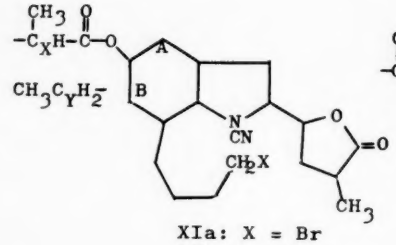
VIb



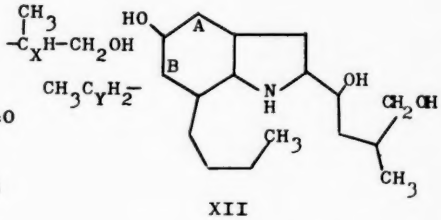
VII



X



XIa: X = Br
XIb: X = OAc



XII

riate derivatives [7]. Only a hydrogen ortho to the acetogroup would be expected to be significantly deshielded in the NMR spectrum of VII in $CDCl_3$/HCl. The smaller deshielding effect on a meta or para hydrogen would be compensated by the shielding influence of the alkyl-substituents. The spectrum exhibits, besides ten protons at 2.78 ppm, a one proton singlet at 2.33 ppm corresponding to the expected position of a proton ortho to the aceto group.

Reduction of the ketone of VII with $NaBH_4$ in methanol affords VIII, m.p. 173-176°. IR ($CHCl_3$): ν_{max} 3600, 3400 cm^{-1}.

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[7] K.M.Jackman, Applications of Nuclear Magnetic Resonance Spectroscopy in Organic Chemistry, Pergamon Press, New York, 1959.

UV (ethanol): λ_{max} 254 mμ, ϵ =3900; λ_{max} 269 mμ, ϵ =1850. UV (ethanol/HCl): λ_{max} 253 mμ, ϵ = 1300; λ_{max} 269 mμ, ϵ =1580; λ_{max} 277 mμ, ϵ =1580. The NMR spectrum of VIII has a ten proton peak at 2.78 ppm and a one proton singlet at 3.36 ppm. Such a marked shift toward higher field can only arise if the hydrogen is either ortho or para to the amino group. It follows that the relative position of the aceto- and amino-group has to be meta.

From the acidic fraction γ,γ-diphenyl-ß-methylbutyrolactone (IX) was isolated, m.p. 140-141°. Found: C, 80.25; H, 7.10; O, 12.79; C-CH_3, 5.92; sap. equiv., 255. IR (KBr): ν_{max} 1780, 1605(w) cm^{-1}.

To gain more information about the neighbourhood of the nitrogen, we prepared the pyrrol (X), m.p. 174-177°, already described by Schild[1] and H.Kondo et al.[8] X is formed from tuberostemonine under very mild oxidative conditions. Found: C, 71.02; H, 7.82; O, 17.40; N, 3.87; C-CH_3, 8.63. IR (KBr): ν_{max} 1760 cm^{-1}. UV (ethanol): λ_{max} 234 mμ, ϵ =10900; λ_{max} = 278 mμ, ϵ =1500. The NMR spectrum exhibits a pyrrol ß-hydrogen at 4.08 ppm, split into a narrow doublet (J = 2.2 cps, 1:3 split). One of the secondary γ-lactone hydrogens is further deshielded by the pyrrol nucleus to 4.61 ppm. The γ-hydrogen of the other lactone group appears at 5.39 ppm. A quartet for two C-methyls is placed at 8.54, 8.6, 8.67 and 8.7 ppm. A C-methyl triplet is centered at 8.96 ppm. This NMR spectrum proves that tuberostemonine contains a

[8] H.Kondo, M.Satomi and T.Kaneko, Ann.Rep.ITSUU Lab. 9, 99 (1958).

2,3,5-trisubstituted pyrrolidine ring. However, so far we were unable to provide any data about the nature of the third carbon connected with the nitrogen. The NMR spectrum of the von Braun degradation product of tuberostemonine offers this information and confirms the substitutional pattern ascertained for the two other carbons α to the nitrogen.

Action of BrCN on tuberostemonine gave in our hands compound XIa, m.p. 80-85°. A Japanese group reports the isolation of a substance melting at 200-202° [9]. Found: C, 57.22; H, 7.08; N, 6.23; Br, 18.90; C-CH_3, 6.31. IR (KBr): ν_{max} 2200, 1775 cm^{-1}. We ascribe a multiplet for two protons at 5.52 ppm in the NMR spectrum to the two γ-hydrogens of the lactones. A one hydrogen peak at 6.16 ppm accounts for a proton α to the cyanamide, which is further deshielded by the β influence of one of the lactones. A three proton peak centered at 6.66 ppm represents the second hydrogen α to the cyanamide and the two hydrogens α to the bromine. That this assignment is in fact correct is proven by converting the primary bromide into the primary acetate (XIb) with silver acetate in pyridine. Two of the hydrogens of the 6.66 peak of the bromide spectrum should be shifted down field to approximately 6 ppm. The NMR spectrum of XIb shows indeed two protons at 5.52 ppm, three at 6.03 ppm, and one at 6.67 ppm.

The acetate (XIb) melts at 145-146°. Found: C, 65.13; H, 7.92; O, 21.06; N, 6.11; C-CH_3, 9.28. IR (KBr): ν_{max}

[9] H.Kondo, K.Suzuki and M.Satomi, J.Pharm.Soc.Japan 61, 111 (1941).

2200, 1775, 1725 cm^{-1}.

Finally we performed a modified Kuhn-Roth oxidation [10] on tuberostemonine and on XII, the lithium aluminum hydride reduction product of XIa. Tuberostemonine yields acetic- and propionic acid. XII yields acetic-, propionic-, butyric- and valeric acid, in agreement with the assigned structures I and XII, respectively. The acids were identified in the form of their methyl esters by vapor phase chromatography.

Acknowledgements: M.G. is greatly indebted to Professors K.Wiesner and Z.Valenta for the opportunity to work in their laboratories and for constant encouragement.
A.H.G. wants to acknowledge a NRC studentship.

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[10] H.Bickel, H.Schmid and P.Karrer, Helv. 38, 649 (1955).

Tetrahedron Letters No. 20, pp. 716-717, 1961. Pergamon Press Ltd. Printed in Great Britain.

STEREOISOMERE 1,4-DI-O-METHANSULFONYL-BUTAN-1,2,3,4-TETROLE

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Forschungslaboratorium der Leo Pharmaceutical Products

Dänemark

(Received 10 October 1961)

ZU Untersuchungen auf eine mögliche antineoplastische Wirkung haben wir die stereoisomeren 1,4-Di-O-methansulfonyl-butan-1,2,3,4-tetrole dargestellt. Es handelt sich um D- und L-Threit-1,4-di-methansulfonat (D-I und L-I), deren Racemat (DL-I) und Erythrit-1,4-di-methansulfonat (II). Diese bifunktionell alkylierenden Verbindungen erschienen uns interessant, weil sie sowohl als Methansulfonate als auch hinsichtlich ihrer Kettenlänge mit Myleran ($CH_3.SO_2.O-(CH_2)_4-O.SO_2.CH_3$) verwandt sind. Sie zeigen gegenüber Letzterem ein grösseres und somit vielleicht günstigeres[1] Verteilungsverhältnis zwischen Wasser-Fett. Wegen der in Nachbarstellung zu den Methansulfonyloxygruppen stehenden Hydroxylgruppen können bei bestehender Möglichkeit einer Cycloalkylierung veränderte alkylierende Eigenschaften erwartet werden. Die Stereoisomeren müssen weiterhin in der Reaktion mit Nucleoproteiden voneinander differieren, was zu einer mehr spezifischen biologischen Aktivität führen kann. Es sei darauf hingewiesen, dass über 1,6-Di-O-methansulfonyl-D-mannit bereits von anderer Seite berichtet wurde[2].

D-I, L-I, DL-I und II wurden in 30 proz. Ausbeute durch Ringöffnung der entsprechenden stereoisomeren 1,2;3,4-Dioxido-butane[3] mit Methansulfon-

[1] G.M. Timmis, Ann.N.Y.Acad.Sci. 68 (3), 727 (1958); R.F. Hudson G.M. Timmis und R.D. Marshall, Biochem.Pharm. 1, 48 (1958).

[2] A. Haddow, G.M. Timmis und S. Brown, Nature,Lond. 182, 1164 (1958); L. Vargha und J. Kuszmann, Naturwissenschaften 46, 84 (1959).

säure gewonnen. Die Umsetzung der stereoisomeren 1,4-Dibrom-butan-2,3-diole[3] mit Silbermethansulfonat in Acetonitril lieferte neben Diacetyl ebenfalls ohne Angriff an den Asymetriezentren die gewünschten Methansulfonate in 30 - 40 proz. Ausbeute. D-I: Schmp. 102 - 103°C, $[\alpha]_D^{20}$: + 5,5° (c = 2, Aceton). L-I: Schmp. 102 - 103°C, $[\alpha]_D^{20}$: -5,3° (c = 2, Aceton). DL-I: Schmp. 99,5 - 101°C. II: Schmp. 111 - 114°C (unstabile Kristallform), Schmp. 121,5 - 123,5°C (stabile Kristallform). Über eine weitere Synthesemöglichkeit wird später ausführlicher berichtet werden.

Die Verbindungen werden vom National Cancer Institut unter National Institut of Health, U.S.A. getestet. L-I zeigt im Dunning-Leukämie-Test in Gegensatz zu Myleran eine dem 6-Mercaptopurin entsprechende Wirkung.[4] Klinische Prüfungen sind in Vorbereitung.

[3] P.W. Feit, Chem.Ber. 93, 116 (1960).

[4] R. Jones, Jr., W.B. Kessler, H.E. Lessner und L. Rane, Cancer Chemotherapie Rep. 10, 99 (104, 106) (1960).

Tetrahedron Letters No. 20, pp. 718-719, 1961. Pergamon Press Ltd. Printed in Great Britain.

1961

ISOLATION OF PYRROLE-2,3,4-TRICARBOXYLIC ACID AND PYRROLE-2,3,4,5-TETRACARBOXYLIC ACID FROM SEPIOMELANIN OXIDATION PRODUCTS

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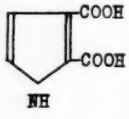
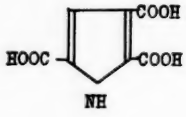
Institute of Organic Chemistry of Naples, Italy

(Received 12 October 1961)

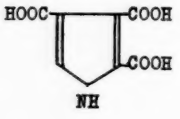
IT is known that only two pyrrolic acids, namely pyrrole-2,3-dicarboxylic acid (I)[1] and pyrrole-2,3,5-tricarboxylic acid (II)[2] have been isolated from the products obtained by oxidation of sepiomelanin with hydrogen



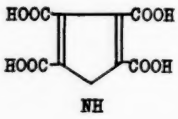
I



II



III



IV

peroxide in alkaline solution. More recently pyrrole-2,3,4,5-tetracarboxylic acid (IV) was identified by paper chromatography after degradation with hydrogen peroxide in acetic acid[3].

[1] R.A. Nicolaus, private communication.

[2] L. Panizzi and R. Nicolaus, Gazz.Chim.Ital. 82, 435 (1952).

[3] R.A. Nicolaus, A. Vitale and M. Piattelli, Rend.Acc.Sc.Fis. e Mat. XXV, 220 (1958).

The product to be expected from the structure assigned to melanins by Harley-Mason,[4] pyrrole-2,3,4-tricarboxylic acid (III), was never recognized.

In pursuing our work concerned with the elucidation of sepiomelanin structure, we succeeded in isolating both pyrrole-2,3,4-tricarboxylic acid and pyrrole-2,3,4,5-tetracarboxylic acid from the mixture of oxidation products of sepiomelanin; however, it should be emphasized that the former was obtained in extremely low amount.

Sepiomelanin was oxidized with hydrogen peroxide in acetic acid at room temp. for 12 days. Excess hydrogen peroxide was destroyed by adding sulphur dioxide and the previously concentrated solution was extracted with ether.

A partially purified mixture of III and IV was obtained by counter-current distribution between water and ether (150 stages), which removed I, II and part of the remaining oxidation products. This mixture was further purified by successive paper chromatographic separations (Whatman 3MM) using first propanol-ammonia-water (60:30:10) and then butanol-acetic acid-water (60:15:25) as solvents. The zone containing III and IV was eluted with water, the acid IV was precipitated as monopotassium salt by KCl addition and from the mother liquors the acid III was isolated by paper electrophoresis (electrolyte: pyridinium acetate 0.05 M). The acid IV was obtained from the potassium salt by a strongly acidic ion exchange resin.

These acids were identified by comparing their infra-red spectra, chromatographic and electrophoretic behaviour with those of authentic specimens.

Further details will be published elsewhere.

Acknowledgements - This investigation was supported by the National Cancer Institute, research Grant C-5220 and C1-5220, Public Health Service, U.S.A.

[4] R.I.T. Cromartie and J. Harley-Mason, Biochem.J. 66, 713 (1957).

Tetrahedron Letters No. 20, pp. 720-723, 1961. Pergamon Press Ltd. Printed in Great Britain.

AN UNUSUAL RING CLEAVAGE: FORMATION OF OCTA-2,4,6-TRIEN-1,8-DIAL FROM TRANS-7,8-DIACETOXYBICYCLO[4,2,0]OCTA-2,4-DIENE

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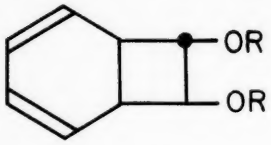
(Received 23 October 1961)

COPE et al.[1] prepared trans-7,8-diacetoxybicyclo[4,2,0]octa-2,4-diene (I), m.p. 62°, by mercuric acetate oxidation of cyclooctatetraene. The structure of I was proven by hydrogenation to a tetrahydro derivative, followed by hydrolysis to a saturated glycol identical with an authentic specimen of trans-7,8-dihydroxybicyclo[4,2,0]octane synthesized from cis-hexahydrophthalic acid. We have found that the NMR spectrum[2] of I (60 Mc/s) has two methyl bands (τ, 8.00, 7.95) thus confirming the trans disposition of the acetoxy groups. No detectable amount of the isomeric 1,2-diacetoxycycloocta-3,5,7-triene was present even after refluxing I in benzene for 1 hr.

In connection with other work, we were interested in obtaining the unsaturated glycol (II) itself, the preparation of which has not been reported. Alkaline hydrolysis of I gave only intractable material, which, however, was observed to give an immediate crimson precipitate with 2,4-dinitrophenylhydrazine reagent. As it was suspected that the carbonyl compound formed was undergoing further condensation under the reaction conditions, a lithium aluminium hydride cleavage of I was tried. Reaction

[1] A.C. Cope, N.A. Nelson and D.S. Smith, J.Amer.Chem.Soc. 76, 1100 (1954).

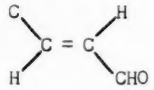
[2] L.M. Jackman, Applications of Nuclear Magnetic Resonance Spectroscopy in Organic Chemistry. Pergamon Press, London, New York (1959).



I, R = $COCH_3$

II, R = H

III

at 25° for 2 min in ether gave, on normal working up, not II, but variable quantities of a crystalline compound III. This was found to be an α:β-unsaturated carbonyl compound from its infra-red spectrum (C=O at 1680 cm^{-1}, C=C at 1624, 1610 cm^{-1}, no OH absorption), and from the NMR spectrum ($CDCl_3$ soln.) the carbonyl function was found to be aldehydic (doublet, 0.27τ, J, 7.2 cps). All the other protons were olefinic (2.6-3.8τ), a quartet centred on 3.8τ was due to the proton coupled with the aledhyde proton. In addition to the 7.2 cps spacing, it showed a spacing of 14.1 cps, which must be due to coupling with a proton situated trans on the double bond. This is similar to the coupling present in trans-croton-aldehyde.[3] The partial structure  was therefore indicated. The olefinic protons at lower field could not be analysed satisfactorily by first order treatment, but intensity measurements showed that the ratio of the olefinic protons: aldehyde proton was 3:1. Clearly, III was formed by a facile oxidation of some intermediate produced during the lithium aluminium hydride cleavage.

By suitably modifying the working up conditions, viz. addition of excess ethyl acetate to the ether slurry, followed by washing the organic layer with dilute phosphoric acid and then with 2% sodium hydroxide, the

[3] J.A. Pople and T. Schaefer, Molec.Phys. 3, 547 (1960).

1961

yield could be improved to 50-60%. Rapid crystallisation from methylene chloride-petroleum ether at -70°C gave an analytical sample of III, as pale yellow needles, m.p. 140° (d) (Found C, 70.02, H, 6.03; $C_8H_8O_2$ requires C, 70.57, H, 5.88%). The compound was not very stable in air and was detectably altered to less soluble material in a few hours. On hydrogenation (ethyl acetate/Pd black) 3 moles of hydrogen were taken up smoothly in 15 min. The product (C=O at 1720 cm^{-1}) was oxidized by bromine water in presence of sodium bicarbonate to an acid, m.p. 140°, in good yield. The latter was identical (mixed m.p., infra-red spectrum) with an authentic sample of suberic acid, $COOH(CH_2)_6COOH$.

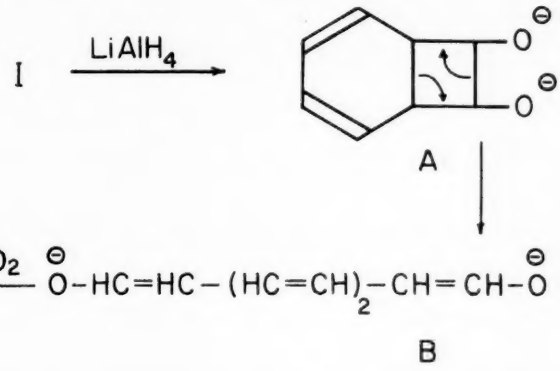
The above evidence defined the structure of III as octa-2,4,6-trien-1,8-dial, with the 2- and 6- double bonds in the trans configuration. It only remained to determine the geometry of the central double bond. This was found to be also trans by the close similarity of the ultra-violet spectrum of III, (λ_{max}^{MeOH} 313 mμ log ε, 4.59, shoulder at 319 mμ, log ε, 4.56) with that of all-trans-2,4,6-octa-trienal[4] (λ_{max}^{EtOH} 315 mμ, log ε, 4.57). It has been pointed out by Braude[5], that in conjugated systems terminated by two oxygen atoms, only one of the carbonyl functions takes part in spectral conjugation. Furthermore, III failed to isomerize in presence of iodine.

The formation of the unsaturated dialdehyde from I can be rationalised as follows. Cleavage with lithium aluminium hydride would be expected to give dianion A. Increase in resonance in going from A to B, and charge repulsion in A may provide sufficient driving force for the ring cleavage to dianion B. This change can be considered as the reverse of ring formation

[4] E.R. Blout and M. Fields, J.Amer.Chem.Soc. 70, 189 (1948).

[5] E.A. Braude in Determination of Organic Structures by Physical Methods (Edited by Braude and Nachod) p. 148. Academic Press, New York (1955).

by a "four-centre-type" reaction.[6] Protonation of B might take place at



various sites to give a vinylogous ene-diol, a diene aldehyde or a triene-aldehyde-alcohol, all of which should be readily oxidizable to III. Indeed, the ethyl acetate solution (prior to shaking with alkali in air), from the lithium aluminium hydride reaction, contained a strongly reducing species as indicated by a positive test (red colour) with 2,3,5-triphenyltetrazolium chloride.[7] This test was negative for III itself.

It seems unlikely that the cleavage takes place through a cyclooctatriene intermediate, as the conversion of bicycloocta[4,2,0]-2,4-diene to cyclooctatriene does not proceed below 30°.[8] Furthermore, there is no particular driving force for this change in the present case.

It is of interest that irradiation of I is reported[9] to give all-trans-1,8-diacetoxyocta-1,3,5,7-tetraene; the compound does not seem to have been characterized beyond its ultra-violet spectrum.

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[6] J. Hine, Physical Organic Chemistry. McGraw-Hill, Book Co. Inc., New York (1956).

[7] W.J. Mador and R.R. Buck, Analyt.Chem. 24, 666 (1952).

[8] A.C. Cope, A.C. Haven, F.L. Ramp and E.R. Trumbull, J.Amer.Chem.Soc. 74, 4867 (1952).

[9] D.H.R. Barton, Helv.Chim.Acta 42, 2604 (1959).

Tetrahedron Letters No. 20, pp. 724-729, 1961. Pergamon Press Ltd. Printed in Great Britain.

1,2-UMLAGERUNG VON PHOSPHOR ZU KOHLENSTOFF

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(Received 23 October 1961)

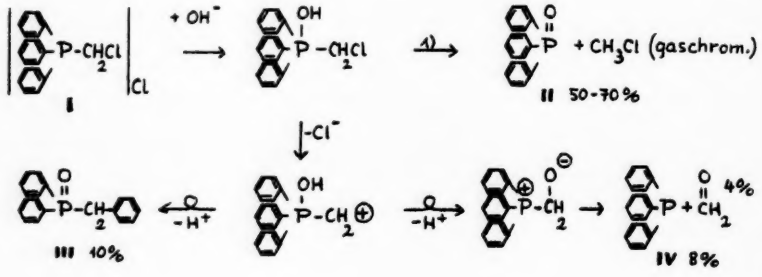
Der Abbau von Phosphoniumsalzen durch Basen kann nach bisherigen Erfahrungen drei Wege einschlagen:

1) Spaltung der Phosphoniumbase in Phosphinoxyd und Kohlenwasserstoff. Nach Ingold[1] wird dabei ein Übergangszustand mit pentakovalentem Phosphor durchlaufen.

2) α-Eliminierung von Wasserstoff, die zum Phosphinalkylen (G.Wittig[2]) führt.

3) β-Eliminierung von Wasserstoff und Zerfall in Phosphin und Olefin.

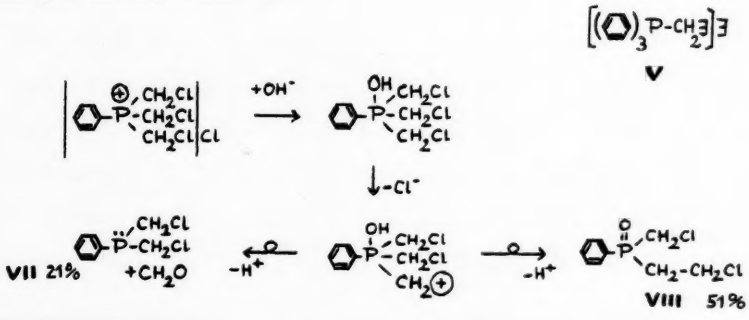
In wasserhaltigen Lösungsmitteln stellt der zuerst genannte den Regelfall dar. Es wurde nun gefunden, daß Halogenmethyl-phosphoniumsalze in Wasser noch einen ganz anderen Abbau erleiden können, der mit dem unter 1) genannten konkurriert und möglicherweise den gleichen Übergangszustand passiert. Die erhaltenen Ergebnisse und eine vorläufige Deutung sind nachstehend durch Formeln wiedergeben. Z.B. bildet I nebeneinander II, III und IV:



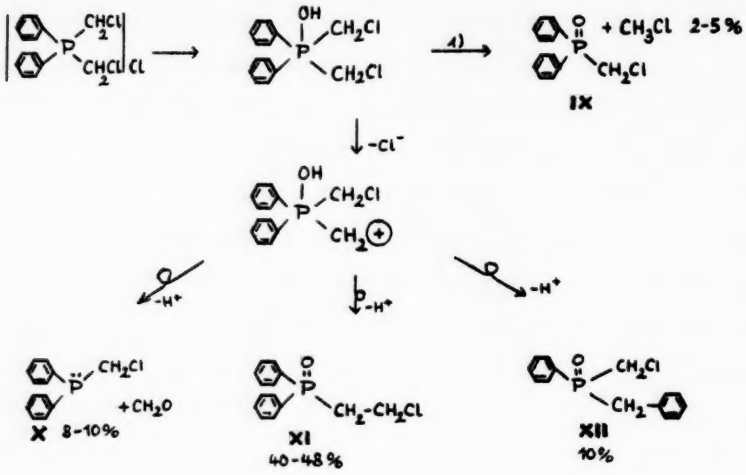
Offenbar wird α-ständiges Halogen aus einem pentakovalenten Übergangszustand abgespalten (in Konkurrenz zur Eliminierung von Methylchlorid), worauf einer der anderen Liganden unter Lösung der Bindung zum Phosphor in die entstehende Lücke einrücken kann. Ob auch Hydroxyl in der formulierten Weise intramolekular wandert, ist noch nicht mit Sicherheit zu entscheiden, jedoch in Anbetracht der weitgehenden p_H-Unabhängigkeit des Ausbeuteverhältnisses III : IV denkbar. Eine weitergehende Aussage ist erst nach Abschluß der reaktionskinetischen Untersuchung möglich, die zur Zeit im Gange ist.

Halogeneliminierung und Umlagerung scheinen gekoppelte Vorgänge zu sein, denn das analoge Jodmethyl-Salz V liefert zwar ebenfalls III (Phenyl wandert), aber kein IV. V entsteht aus Triphenylphosphin und Dijodmethan in Dimethylformamid mit 70% Ausbeute (von Michaelis[3] irrtümlich als $\left[(C_6H_5)_3\overset{+}{P}\text{-}CH_2\text{-}\overset{+}{P}(C_6H_5)_3\right]J_2$ beschrieben).

In den folgenden Beispielen ist der Abbau nach 1) fast vollständig unterdrückt. Sie zeigen, daß der elektronegativere Ligand (Chlormethyl) leichter wandert:



[1] C.K.Ingold, J.Chem.Soc. 1929, 2342; 1933, 531.
[2] G.Wittig, Angew.Chemie 68, 505 (1956).
[3] A.Michaelis und Gleichmann, Ber.dtsch.Chem.Ges. 15, 801 (1882).



Da kürzlich über eine ähnliche Hydridwanderung bei Chlormethyl-dimethylsilan[6] und bei Chlormethylphosphonigsäure[7] berichtet wurde, scheint es sich um eine Reaktion allgemeinerer Art zu handeln, die wir weiter verfolgen.

Strukturbeweise und Daten der Verbindungen VII bis XII:

IX (Fp. 138-140°) und XI (Fp. 125-127°) wurden auf einem zweiten, strukturell eindeutigen Wege aus $(C_6H_5)_2P(O)CH_2OH$ (siehe unten) bezw. $(C_6H_5)_2P(O)CH_2\text{-}CH_2OH$[8] und Phosphorpentachlorid dargestellt. Die Oele VII und X wurden durch folgende Reaktionen charakterisiert (Ausbeuten 80-90%): Bei der Oxydation mit Peressigsäure ging VII in das bekannte $C_6H_5P(O)(CH_2Cl)_2$[9] (VIIa, Fp. 142°), X in IX über. Triäthyloxonium-fluoborat lieferte aus VII $\left[C_6H_5P(CH_2Cl)_2C_2H_5\right]BF_4$[10] (VIIb, Fp.105-107°),

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[6] L.H.Sommer, W.P.Barie und D.R.Weyenberg, J.Amer.Chem.Soc. 81, 251 (1959).
[7] E.Uhing, K.Ratenbury und A.D.F.Toy, J.Amer.Chem.Soc. 83, 2299 (1961).
[8] K.Issleib und H.M.Möbius, Chem.Ber. 94, 102 (1961).
[9] L.M.Yagupolski und P.A.Yufa, Z.obsh.Kim.SSSR 28, 2853 (1958).
[10] Dissertation O.Schumacher, Tübingen 1961.

aus X $\left[(C_6H_5)_2P(CH_2Cl)(C_2H_5)\right]BF_4$[10] (Xb, Fp. 129-130°). VIIb und Xb wurden von O.Schumacher[10] auch auf unabhängigem Wege aus Phenyl-äthyl-phosphin bezw. Diphenyl-äthyl-phosphin in üblicher Weise dargestellt[13] (CH_2O + HCl liefert das Hydroxymethyl-phosphoniumsalz, das mit Thionylchlorid chloriert und mit $AgBF_4$ in das Fluoborat überführt wird).

Die Strukturen von VIII und XII wurden aus den IR-Spektren und Analysen erschlossen. (VIII: Fp. 68-70°; gefunden C 45,60; H 4,52; P 12,86; Cl 29,76; berechnet für $C_9H_{11}Cl_2OP$: C 45,58; H 4,68; P 13,08; Cl 29,91. XII: Fp. 132-133°; gefunden C 63,94; H 5,10; P 11,77; Cl 13,32; berechnet für $C_{14}H_{14}ClOP$: C 63,54; H 5,35; P 11,72; Cl 13,42). VIII zeigt die qualitativ gleichen IR-Hauptabsorptionen wie VIIa und IX, ($\tilde{\nu}_{max}^{KBr}$: 1112, 1143, 1191 (P=O), 1227, 1400, 1438 (P-C_6H_5) cm^{-1}), aber zusätzlich zwei starke Banden bei 1026 und 1307 cm^{-1}, die ebenso bei XI auftreten, hingegen nicht bei II, III und XII. XII stimmt mit III im Bereich von 900 bis 1600 cm^{-1} qualitativ überein (charakteristisch für die Benzylgruppe: 909(III) bezw. 916(XII), 1240, 1250, 1450, 1494 cm^{-1}).

Aus $\left[C_2H_5\text{-}P(CH_2Cl)_3\right]BF_4$ erhält man durch Alkaliabbau Äthyl-bis-chlormethyl-phosphin $C_2H_5\text{-}P(CH_2Cl)_2$ (IXX) in 71-76% Ausbeute ($Sdp._5$ 55-57°). Die Chlormethylphosphine VII, X und IXX sind unbeständig. Ihre geringe Reaktionsbereitschaft gegenüber Schwefel und Alkylierungsmitteln ist auffällig.

In den Phosphinoxyden reagiert β-ständiges Chlor normal, α-ständiges hingegen ist erwartungsgemäß durch die Phosphinylgruppe desaktiviert und schwerer zur Reaktion zu bringen[11,12].

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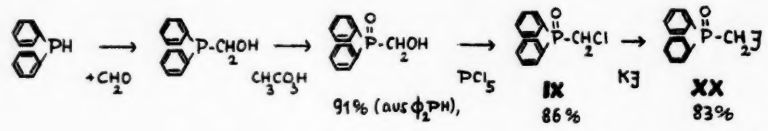
[11] A.Hoffmann, J.Amer.Chem.Soc. 52, 2997 (1930).

[12] H.Hoffmann, L.Horner, H.Ertel und G.Klahre, Tetrahedron Letters 1961, 9.

[13] H.Hellmann und O.Schumacher, Angew.Chemie 72, 77 (1960).

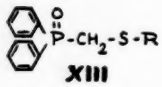
Mono-halogenmethyl-phosphinoxyde erhält man auf diesem und einigen anderen Wegen schlecht (vgl. auch Kosolapoff und Struck[14]), hingegen leicht auf folgende Weise:



Fp.136-7° Fp.138-140° Fp.186-188°

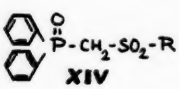
(Gefunden für XX: C 45,80, H 3,37, J 36,57, P 9,15. Berechnet für $C_{13}H_{12}JOP$: C 45,65, H 3,54, J 37,10, P 9,06).

IX reagiert bei 30-60° in Alkohol rasch mit Thiolaten zu Sulfiden XIII, die mit Peressigsäure α-Sulfonyl-phosphinoxyde XIV liefern:



XIII

R	Fp.	Ausbeute
a) CH_3	139-140°	87%
b) n-C_3H_7	112-113°	91%
c) CH_2-C_6H_5	134-136°	95%
d) C_6H_5	101-102°	75%



XIV

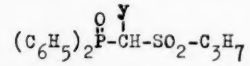
R	Fp.	Ausbeute
a) CH_3	203-205°	85%
b) n-C_3H_7	157-158°	83%
c) CH_2-C_6H_5	221-222°	93%
d) C_6H_5	180-181°	71%
e) C_6H_4-CH_3	169-172°	62%

(Repräsentative Analysendaten: XIIIa; gefunden: C 64,10, H 5,71, P 12,15; Berechnet für $C_{14}H_{15}POS$: C 64,10, H 5,77, P 11,84.- XIVd; gefunden: C 64,13, H 4,62, S 8,77, P 8,51; berechnet für $C_{19}H_{17}PO_3S$: C 64,03, H 4,82, S 8,98, P 8,70).

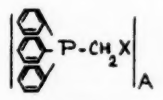
α-Sulfonyl-phosphinoxyde XIV bilden mit Kaliummetall in Dioxan

[14] G.M.Kosolapoff und R.F.Struck, J.Chem.Soc. 1961, 2423.

Kaliumsalze, die durch Alkylhalogenide glatt alkyliert werden, z.B. XIVb mit Benzylbromid zu XV (Fp. 217-219°, Ausbeute 61%. Gefunden: P 7,54, S 7,80. Berechnet für $C_{23}H_{25}O_3PS$: P 7,52, S 7,77). In Gegenwart katalytischer Mengen der Kaliumsalze wird Acrylnitril addiert, z.B. zu XVI (Fp. 165-167°). Natronlauge spaltet XIVc in Diphenylphosphinsäure und Methyl-benzyl-sulfon, während aus dem homologen XVII (Fp. 202-203°; aus XI analog XIV gewonnen) Benzylsulfinat abgespalten wird.

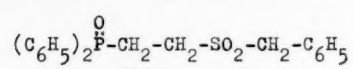


XV: y = CH_2-C_6H_5
XVI: y = CH_2-CH_2CN



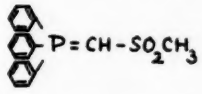
XVIII

a) X = OCH_3 [15]
b) X = SCH_3 [15]
c) X = SO_2CH_3, Fp. 210-213°.



XVII

XXI



Die Phosphoniumsalze XVIIIa - c lagern sich beim Alkaliabbau nicht um. XVIIIa liefert $(C_6H_5)_2P(O)CH_2$-OCH_3, XVIIIb hingegen $(C_6H_5)_3PO$. Da O elektronegativer ist als S, fügt sich dieser Befund nicht in die Ingold'sche Regel ein. XVIIIc ergibt mit wässriger Natronlauge das luftbeständige Phosphinalkylen XXI (Fp. 201-203°, Ausbeute 65%. max 950-980, 1098-1110, 1260, 1482 cm^{-1}. Gef.: C 67,80, H 5,90, S 8,89, P 8,56. Berechnet für $C_{20}H_{19}O_2PS$: C 67,78, H 5,41, S 9,04, P 8,76). Dieses Ergebnis, ebenso wie die Synthese eines stabilen α-Phosphinyl-phosphinalkylens durch F.Ramirez und Mitarbeiter[16] bestätigen den Befund von L.Horner[17], daß die Stabilisierung von Phosphinalkylenen auch durch den induktiven Effekt möglich ist.

Wir danken dem Fonds der Chemischen Industrie und der Deutschen Forschungsgemeinschaft für finanzielle Unterstützung, den Farbenfabriken Bayer, der Badischen Anilin- und Sodafabrik und den Farbwerken Hoechst für die großzügige Ueberlassung von Chemikalien.

[15] G. Wittig und M. Scklosser, Chem.Ber. 94, 1381 (1961).

[16] F. Ramirez, N.B. Desai, B. Hansen und N.Mc. Kelvie, J.Amer Chem.Soc. 83, 3539 (1961).

[17] L. Horner und H. Oediger, Chem.Ber. 91, 438 (1958).

Tetrahedron Letters No. 20, pp. 730-734, 1961. Pergamon Press Ltd. Printed in Great Britain.

SCHIZANDRIN - LIGNAN OF UNUSUAL STRUCTURE

N.K. Kochetkov, A. Khorlin, O.S. Chizhov and V.I. Sheichenko

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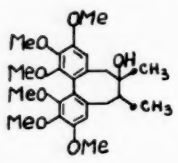
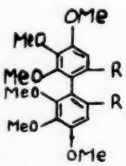
Academy of Sciences, Moscow

(Received 24 October 1961)

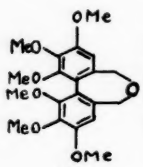
WE have recently described[1] the isolation and some properties of schizandrin, schizandrol and γ-schizandrin - Schizandra chinensis Baill. seed oil components. The present communication contains data, which may serve as basis for suggesting structure (I) for schizandrin.



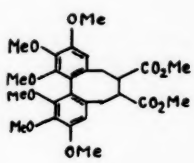
I



IIa R = COOH
IIb R = $COOCH_3$
IIc R = CH_2Br



III



IV

Schizandrin has the molecular formula $C_{24}H_{32}O_7$ * (Found C, 66.44, 66.52; H, 7.20, 7.39; OCH_3 41.75, 41.50; C-CH_3 5.54, 5.56. Calc. C, 66.65; H, 7.46; 60 CH_3 43.05; 2 C-CH_3 6.95). Schizandrin I.R.-spectrum contains a sharp hydroxyl band (3495 cm^{-1}). This hydroxyl is inert towards CrO_3 in CH_3COOH and acetic anhydride in pyridine which is an indication of its tertiary character. $KMnO_4$-oxidation of schizandrin in 2% KOH for 48 hours at 50° gave an aromatic dicarboxylic acid $C_{20}H_{22}O_{10}$, m.p. 240-242°, R_f 0.10

* The previously published analytical data were not exact.[1]

[1] N.K. Kochetkov, A. Khorlin and O.S. Chizhov, J.Gen.Chem. (U.S.S.R.) 31, 3454 (1961).

(butanol - 1.5 N ammonia 1:1), dimethyl ester m.p. 93-95°. Hathway[2] gives m.p. 243° for 4,5,6,4',5',6'-hexamethoxydiphenic acid (IIa) and for the dimethyl ester (IIb) m.p. 95-97°. Mixed melting point, I.R.- and U.V.-spectra, paper chromatography (R_f-value and colour of spots by detection with Male reagent) and thin non-fixed layer chromatography on alumina of the dimethyl ester showed our products to be completely identical with specially prepared samples of IIa and IIb.

The 2,2'-hydrogens of the diphenyl nucleus in the schizandrin molecule could have been substituted either by short side chains or by a two-, three- or four-membered bridge. The choice between these structures was made on the basis of the U.V.-spectrum of schizandrin. Turner et al.[3] showed, that the U.V.-spectra of the biphenyl derivatives, containing a bridge between the 2,2'-positions, depend upon the number of members in the cycle. Absorption peaks, arising from the aromatic rings conjugation, shift in the direction of smaller wavelengths and become flatter on passing from an eight-membered to a six-membered cycle. There is also a concurrent narrowing of the longer-wave peak. Furthermore, unbridged biphenyl derivatives, substituted in the 2,2'- and 6,6'-positions are known to have no conjugation peaks.[4]

Schizandrin U.V.-spectrum was similar to that of dimethyl-1,2,3,4-dibenzocyclooöcta-1,3-dien-6,7-dicarboxylate. In order to exclude any violation of the above mentioned regularities, which could have been caused by the presence of six methoxyls, we synthesized a number of more suitable model compounds, namely, 1,2,3,8,9,10-hexamethoxy-5,6-dihydrophenantrene

[2] D.E. Hathway, J.Chem.Soc. 519 (1957).

[3] G.H. Beaven, G.R. Bird, D.M. Hall, E.A. Johnson, J.E. Ladbury, M. Leslie and E.E. Turner, J.Chem.Soc. 2708 (1957) and other parts of the series.

[4] B Williamson and W.H. Rodebush, J.Amer.Chem.Soc. 63, 3018 (1941).

(V), hexamethoxydihydrodibenzoxepin (III) and dimethylhexamethoxy-dibenzocyclo-octadien-6,7-dicarboxylate (IV).*

The U.V.-spectra of these compounds as well as of schizandrin are shown in Figs. 1 and 2. There is a close similarity between the U.V.-spectra of schizandrin and compound IV, whereas all the other substances differ from the former.

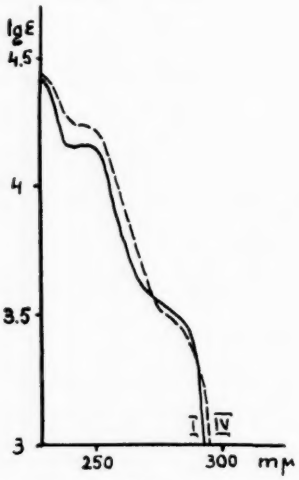


Fig. 1.

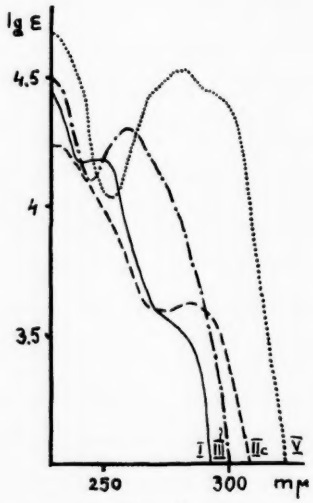
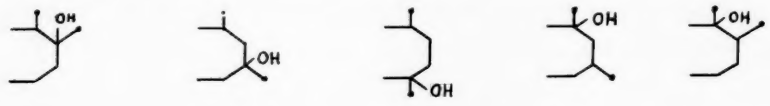


Fig. 2.

Schizandrin is thus a dibenzocyclo-octadiene derivative. It follows, that besides structure I five other structures are possible. As the



VI VII VIII IX X

hydroxyl is not affected by hydrogenolysis, formulae VIII-X seem less probable.

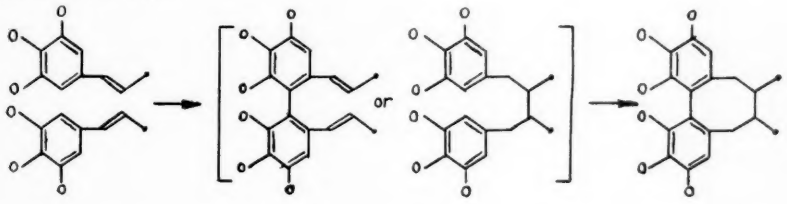
Structure I was confirmed by the NMR-spectrum of schizandrin**, which

* The synthesis will be described elsewhere.

** The NMR-spectrum was observed at 40 Mc in carbon tetrachloride solution vs. benzene as an external etalon.

exhibited peaks, characteristic of aromatic hydrogens(16.4 and 18.8 cps), methoxyl (129 and 140 cps), methyl (235, 249 and 255 cps), hydroxyl (214 cps) and methylene (182 and 187 cps). The most essential information for the choice between the structures VI-X and I was obtained from the analysis of the width and position of the methylene peaks. The area of this wide doublet corresponds to four protons. The chemical shift corresponds to alkylbenzene CH_2-groups. The considerable width of the doublet is due to difference in the position of protons at the hydroxyl, as well as to axial equatorial hydrogens shift and spin-spin splitting. By no means does this doublet correspond to chemical shift between the methylene groups of structures VI, VII, IX and X, which should have led to a distance of 35-40 cps between the peaks[5].

Though the structure of I is rather uncommon, its biosynthesis can be well imagined to proceed through dimerization of a precurser of the isoelemicyne type:



Structures VI-X, on the other hand, cannot be explained from the biogenetic viewpoint without additional assumptions.

Schizandrin is the first representative of the new type of lignans, characterized by an aryl-aryl bond and an eight-membered ring.

γ-Schizandrin and schizandrol, isolated from Schizandra chinensis, have U.V.-spectra, quite similar to that of schizandrin, and presumably contain the same 1,2,3,4-dibenzocyclooöcta-1,3-diene system. It is known,

[5] N.F. Chamberlin, Analyt.Chem. 31, 56 (1959).

that seven-membered cycles are sometimes formed by oxidative coupling of phenols, but we believe this to be the first case of such a pathway for an eight-membered cycle.

Acknowledgements - Our grateful thanks are due to M. Grachev translating this article.

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ERRATUM

H.J. BESTMANN und B. ARNASON: C-Acylierung von Triphenylphosphin-Alkylen mit aktivierten Estern, Tetrahedron Letters No. 14, 455-457 (1961).

The sentence below should have followed the first paragraph on p. 455 of the above article.

"Besonders geeignet für die Acylierung sind Carbonsaure-S-Thioäthylester."

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MUTAROTATION AND ISOMERIZATION OF IMINES

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(Received 10 November 1961)

CURTIN and HAUSSER,[1] have recently reported the interconversion of stereoisomeric N-methyl and N-aryl-imines derived from p-substituted benzophenones. The changes take place on standing or in solution in cyclohexane and at rates which vary greatly with the nature of the N-substituent. According to these authors "there seem to be no (previous) cases where true steroisomerism (of imines) has been demonstrated unequivocally". In this connexion we wish to report further data on the behaviour of N-(1-phenylalkyl)-1-phenylakylidenimines,[2] for which two tentative explanations have been advanced, including a cis-trans (sin-anti) isomerization similar to that proposed by Curtin and Hausser.

We have been studying for several years the ethoxide ion catalyzed prototropic change of N-benzyl-benzylidenimine and its alkylderivatives in ethanol-dioxane:

$$\underset{\text{A}}{\text{Ph-CHR-N=CR'-Ph}} \rightleftharpoons \underset{\text{B}}{\text{Ph-CR=N-CHR'-Ph}}$$

[1] D.Y. Curtin and J.W. Hausser, J.Amer.Chem.Soc. 83, 3474 (1961).

[2] R. Perez Ossorio and V. Sanchez del Olmo, An.Real.Soc.Espan.Fis. y Quim. 56-B, 921 (1960).

(R, R' = H or alkyl)[3]. When in A, R = alkyl and R' = H, the rate of the forward change A ⟶ B was followed, in some instances[3a,j] by the loss of optical activity of the system starting with optically active A[4]. As A looses its activity on tautomerization to racemic B which, in turn, reverts to racemic A, the optical activity of the system approaches zero. However, when the tautomerization of N-(1-phenylethyl)-1-phenylethylidenimine (A = B, R = R' = Me) was attempted, the optical activity of the solution decreased slightly and approached a limiting value. It was subsequently shown that imines in which both R and R' were alkyl groups did not give the prototropic change, under the conditions in which N-benzyl-benzylidenimine and its monoalkylderivatives do. The treated dialkylimine behave under polarimetric observations in the same manner as the untreated compound. Therefore rotation changes must be attributed to another origin.[3k]

The optically active imines recorded in Table 1 were next examined: II, III and VII, when polarimetrically observed without solvent, showed mutarotation which was apparently absent in the remaining compounds. In ethanol solution, mutarotation was observed in the same cases as for the pure imines but its direction was reversed: thus, in the dimethyl derivative

---

[3a] R. Perez Ossorio and F. Gomez Herrera, An.Real Soc.Espan.Fis. y Quim. 50-B, 875 (1954); [b] R. Perez Ossorio, F. Gomez Herrera and A. Hidalgo, Ibid. 52-B, 123 (1956); [c] R. Perez Ossorio, F. Gomez Herrera and R.M. Utrilla, Nature.Lond. 179, 40 (1957); [d] R. Perez Ossorio, J.M. Gamboa and R.M. Utrilla, An.Real Soc.Espan.Fis. y Quim. 53-B, 17 (1957); [e] R. Perez Ossorio and A. Alemany, Ibid. 54-B, 471 (1958); [f] R. Perez Ossorio, F. Gomez Herrera, R.M. Utrilla, A. Hidalgo and J.M. Gamboa, Ibid. 54-B, 481 (1958); [g] R.M. Utrilla, Ibid. 54-B, 487 (1958); [h] J.M. Gamboa, R.M. Utrilla and R. Perez Ossorio, Radioisotopes in Scientific Research Vol. II, Proc. First p. 57. UNESCO Int. Conf. Paris, 1957. Pergamon Press, London (1958); [i] F. Gomez Herrera and A. Hidalgo, An.Real Soc.Espan.Fis. y Quim. 55-B, 617 (1959); [j] F. Gomez Herrera, Ibid. 56-B, 909 (1960); [k] R. Perez Ossorio and V. Sanchez del Olmo, Ibid. 56-B, 915 (1960).

[4] See R. Perez Ossorio and E.D. Hughes, J.Chem.Soc. 426 (1952) and references given there.

the rotation increased when observed without solvent and decreased when in ethanol solution.

Table 1

Mutarotation of N-(1-Phenylalkyl)-1-phenylalkylidenimines
Ph-CHR-N=CR'-Ph

Compound	R	R'	Net[a]	Ethanol sol.[a,b]	Ref.
I	Me	H	+34.47 + 34.54	+1.32 + 1.42[c]	3j
II	Me	Me	-35.16 - 39.62	+9.31 + 6.32	2
III	Et	Et	+46.95 - 15.65	+0.72 + 5.05	2
IV	Pr^i	Pr^i	-10.24 - 10.24	-1.88 - 1.87	2
V	Bu^t	Bu^t	+18.15 + 18.14	+3.68 + 3.92[d]	2
VI	Me	Pr^i	-42.94 - 43.05	-	5
VII	Pr^i	Me	- 6.04 - 9.76	-	5
VIII	Me	Ph	+8(±4) + 7.90	+1.24 + 1.21[e]	2

[a] Initial and final observed rotations at constant temperatures are given.

[b] [imine] = 0.61-0.68 M, T = 32.3o C, α for ℓ = 1 dm.

[c] The small change may be due to solvent evaporation or solvolysis since observations were taken for 1024 hr.

[d] See c; observations taken for 337 hr.

[e] [imine] = 0.39 M, for ℓ = 2 dm.

The next step was the study of mutarotation of II, III, IV and V in different solvents. Some results obtained with II and III are recorded in Table 2; III and IV were tested in four alcohols and no significant change of rotation could be detected.

The observed mutarotations are then dependent of structure and medium

[5] To be published.

It may be argued that the lack of mutarotation can be attributed to the rapid attainement of equilibrium. So with benzene no change was observed with II and III (Table 2) but to decide between an unmeasurably small change and a very rapid one, a recently distilled sample of II, (α_D = + 16.29) and another sample for which equilibrium had been attained, (α_D = + 19.13) were dissolved in benzene and immediately observed under the polarimeter; values of $[\alpha]_D$, + 15.81 and + 15.79 were obtained. With III the recently distilled sample (α_D = + 24.07) gave in benzene $[\alpha]_D$ = - 1.25 and the sample in equilibrium (α_D = - 8.08) gave in benzene solution $[\alpha]_D$ = - 1.01. A rapidly attained equilibrium is suggested. The equilibrium, in other non hydroxylic solvents, was also reached very rapidly.

Two possible interpretations have been contemplated: a cis-trans isomerization:

As III changes much more slowly than II, both without solvent and in the alcohols, IV and V might change at an unobservable slow rate due to steric reasons. Furthermore VI would behave as IV and VII as II. I might change very rapidly. VIII was tested as control, since no cis-trans isomerism is possible; in spite of experimental difficulties for the polarimetric observation it appears to show no mutarotation. N-(1-phenylethyl)-cyclohexylidenimine and cyclopentylidenimine could also be used as controls; but attempts to isolate these imines in pure condition failed.

The possibility of an imine-enamine tautomerism, which does not affect the asymmetric carbon atom, was also considered:

This is in agreement with the lack of mutarotation of the ditert-butyl-derivative but does not explain the behaviour of the di-isopropylimine. Some data about this tautomerism can be found in the literature.[6] However, attempts to isolate derivatives of enamine failed or yielded no clear-cut results.

Table 2

Mutarotation of N-(1-Phenylakyl)-1-phenylaklylidenimines in Different Solvents

Solvent	Compound II[a]	Compound III[a]
MeOH	-3.92[b] - 2.22	-2.35[d] - 4.58
EtOH	+9.31 + 6.32	-0.83[d] - 3.58
Pr^iOH	-6.39[b] - 4.20	-0.51[d] - 5.13
Bu^tOH	-7.86[b] --6.03	+1.13[d] - 0.71
C_6H_6	+2.10 + 2.08	-0.16 - 0.17
$CHCl_3$	+3.19[c] + 2.98	-0.28[e] - 0.85
C_5H_5N	+4.01[c] + 3.90	+1.20[e] + 2.21
CCl_4	+3.40[c] + 3.10	+0.90[e] - 0.50
CH_3CO_2Et	+2.35[c] + 2.21	+1.50[e] + 0.64

[a] Initial and final rotations at constant temperatures are given: [imine] 10%, α for l = 1 or 2 dm.

[b] Solutions prepared from a sample of II which, after mutarotation without solvent gave α = -26.96.

[c] See b; α = +13.30 for pure imine.

[d] See b; α = +10.01 for pure imine.

[e] See b; α = + 8.19 for imine.

6[a] A. Seher, Arch.Pharm. 284, 371 (1951); Chem.Abstr. 2124 (1953);

[b] W. Krabbe, E. Polzin and A. Seher, Ber.Dtsch.Chem.Ges. 74-B, 1892 (1941).

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The mutarotation of II is slow enough to allow spectroscopic observation long before equilibrium is reached. The infra-red spectrum of recently distilled II and that of II in equilibrium show the same bands, but small differences in intensity are apparent at 1660, 1035 and 928 cm^{-1} among others; no frequency asignable to the NH group could be detected. II was then disolved in ethanol and the ultra-violet spectrum of the solution was taken both immediately and after a time long enough for the equilibrium in solution be attained; the maximum at λ,238mμ gave, respectively, log ε,3.98 and 3.95; the small change in intensity could be reproduced.

Table 3

Ultra-violet Spectra of N-(1-Phenylalkyl)-1-phenyl-alkylidenimines, Ph-CHR-N=CR'-Ph

Compound	R	R	λ_{max}(mμ)	log ε
IX	H	H	248	4,28
I	Me	H	248	4,28
X	H	Me	241	4,11
II	Me	Me	240	4,10
III	Et	Et	238	3,98
IV	Pr^i	Pr^i	(238)[a]	(3,56)

[a] No maximum. Absorption taken at the recorded λ.

Finally, assignment of the predominant configuration of imines in ethanol may tentatively be based on their ultra-violet spectra. These spectra show a single maximum recorded in Table 3. In the series N-benzyl-benzylidenimine IX, and its dialkylderivatives II, III, IV, the bathochromic shift and specially the decrease in intensity may be attributed to increasing steric inhibition of the resonance between the C = N bond and the

attached phenyl group. The identity of spectra of IX and I (and of X and II) may mean that a trans configuration is predominant in the ethanol solution.

All these results which are still being completed, and will be published in more detail elsewhere, suggest that a case of stereoisomerism, similar to that described by Curtin and Hausser may be under observation.

This research has been supported in part by the "Fundacion Juan March" to which grateful acknowledgement is made.

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A CONTRIBUTION TO THE STUDIES OF ELIMINATION REACTIONS OF MANNICH BASES, USING POLAROGRAPHIC METHOD

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Polarographic Institute, Czechoslovak Academy of Science, Prague

(Received 2 November 1961)

DURING the study of the mechanism of alkylation by Mannich bases, the elimination reaction of 2-piperidinomethylcyclopentanone and of ω-piperidinopropiophenone and its methoiodide was studied. The polarographic method enabled us to follow the change of concentration with time of both the Mannich base and the resulting α, β-unsaturated ketone from their separated waves. The reaction products were identified by paper and thin layer (alumina) chromatography.

As anticipated the reversible elimination reaction of Mannich bases proceeds by a different mechanism to the irreversible process observed with the corresponding quaternary salt. The isolated elimination reactions were compared by measuring the initial reaction velocities, thus eliminating the effect of the consecutive inactivation of the unstable α, β-unsaturated ketone which is formed. With increasing pH-value, the measured rate constant of the initial reaction follows the course of a dissociation curve in the case of Mannich bases, but increases steadily for the methoiodide. The elimination reaction of Mannich bases is thus not acid-base catalysed, but the elimination step is preceded by a dissociation equilibrium:

$$R\,CO\,CH_2CH_2\,\overset{+}{N}R_2H + B \rightleftharpoons R\,CO\,CH_2\,CH_2\,NR_2 + \overset{+}{B}H$$

$$R\,CO\,CH_2\,CH_2\,NR_2 \overset{\text{unimolecular reaction}}{\rightleftharpoons} R\,COCH = CH_2 + HNR_2$$

This view is substantiated by the coincidence of the potentiometrically measured pK-value with the pH-value at which the rate constant reaches the half of its maximum value, by the slope of the pH-dependence of the rate constant corresponding to a transfer of one proton and finally by the absence of any dependence of the measured rate constant on the type and concentration of the buffer used. The small influence of the ionic strength is also in accordance with the unimolecular rate determining step.

On the other hand, the quaternary salts undergo a generally base catalysed reaction of the type

$$R\,CO\,CH_2\,CH_2\,\overset{+}{N}R_3 + B \xrightarrow[\text{reaction}]{\text{complex}} R\,CO\,CH = CH_2 + NR_3 + \overset{+}{B}H$$

This is manifested (in addition to the difference in the pH-dependence) by the dependence of the measured initial rate constants on capacity and kind of the buffer. The slopes of the linear relationships between rate constants and buffer capacity at given pH-values do not correspond to a simple Brönsted equation. It is thus assumed that a more complicated mechanism than E2 is operating.

A similar behaviour was observed for the elimination reaction of the 6-methylthio-cyclohept-2-en-one, the intermediate in the elimination reaction of thioanalogue of tropinone. Further studies on elimination reactions, Michael addition and the total alkylation reactions of Mannich bases are in progress.

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SYNTHETIC AND POLAROGRAPHIC STUDIES IN THE 3-TROPINONE SERIES

V. Horák and P. Zuman

Department of Organic Chemistry, Charles University and

Polarographic Institute, Czechoslovak Academy of Science, Prague

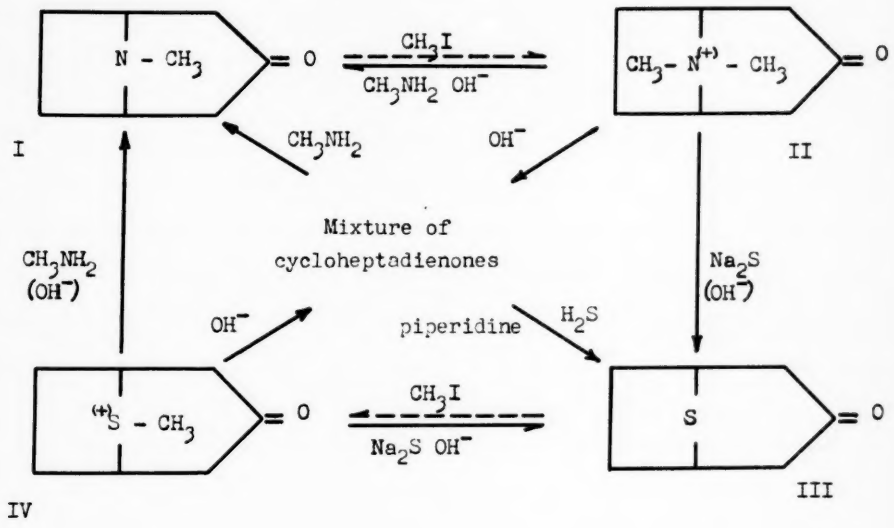
(Received 8 November 1961)

THE reactions of 3-tropinone and its sulphur analogue 8-thia-bicyclo-3,2,1)-octan-3-one represent a complete set of reactions enabling a demonstration of the mutual interrelation of β-amino and β-alkylmercapto ketones in which the reactive components are the corresponding methoiodides II and IV. These are cleavaged in alkaline solutions to yield a mixture of cycloheptadienones. For tropinone methoiodide this particular reaction was described by Meinwald and co-workers.[1] The possible routes of synthetic reactions (partially studied earlier by one of us[2]) can be depicted as shown on page 747 (only the synthetic routes are given, the actual mechanisms of the particular synthetic reaction being more complicated) This scheme clearly shows the relation of all the heterocyclic compounds involved (I-IV) to the mixture of cycloheptadienones (V). The exchange of heteroatoms can occur in all the synthetic reactions via the mixture of cycloheptadienones.

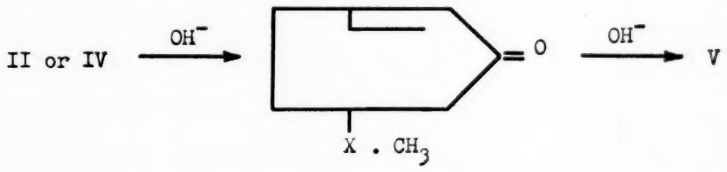
In the formation of V from methoiodides II and IV we were able, using the polarographic method, to prove the existence of 6-dimethylaminocyclohept-2-en-one (VI) and 6-methylmercaptane cyclohept-2-en-one (VII) as inter-

[1] J. Meinwald, S.L. Emerson, N.C. Yang and G. Büchi, J.Amer.Chem.Soc. 77, 4401 (1955).

[2] V. Horák, J. Závada and A. Pískala, Acta Chim.Acad.Sci.Hung. 21, 97 (1959).



mediates. Using polarography optimum reaction conditions were found enabling the isolation of VII.



VI X = NCH_3

VII X = S

Since both VII and its 2,4-dinitrophenylhydrazone and similarly its semicarbazone and thiosemicarbazone are unstable, VII was reduced by sodium borohydride in methanolic solution into corresponding alcohol. This alcohol is an oil distilling (16 mm Hg) at 160-170° (bath temperature), $n_D^{20} = 1.5346$. Its purity was proved by chromatography on thin alumina layer (Al_2O_3 bas.

deactivated with 10% H_2O, chloroform, R_F = 0.5). (Found: C, 60.90; H, 9.06; S, 19.94; H, 0.68 act. Calc. for $C_8H_{14}SO$ (158.26); C, 60.75; H, 8.92; S, 20.24; H, 0.63 act.)

On polarographic curves separate waves for II, V and VI (or IV, V and VII respectively) were found. Whereas the waves for methoiodides II and IV have shown a behaviour similar to that found for other β-aminoketones,[3] the waves for intermediates VI and VII resemble that for simple α, β-unsaturated ketones.[4] Cycloheptadienones V show polarographic curves similar to that of tropone.[5]

From polarographic measurements it was found that the formation of VI from II occurs at pH higher than about 10 whereas cycloheptadienones V are formed from VI at pH higher than about 11. The cycloheptadienones undergo in alkaline solutions above pH 12 a further reaction (isomerisation or dimerisation) resulting in the formation of a polarographically inactive compound (without conjugated system).

On the other hand with the sulphur analogue IV the formation of the intermediate VII occurs at pH above 4. The second elimination step resulting in the formation of V occurs again at pH above 10. Hence the intermediate IV is stable between pH 5 and 9 and under such conditions VII may be isolated by extracting the aqueous solution with ether.

The possibility of mutual interchange of β-aminoketones and β-alkylmercaptanes via the highly reactive onium salts in addition to substitutive demethylation of these compounds is demonstrated here on substances I-IV and seems to have a quite general validity.

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[3] P. Zuman and V. Horák, Advances in Polarography, Proc.IInd Int. Congr. Polarograph., Cambridge 1959 Part II, p. 804. Pergamon Press, London, (1960).

[4] R. Pasternak, Helv.Chim.Acta 31, 753 (1948).

[5] J. Bartek, T. Mukai, T. Nozoe and F. Šantavý, Coll.Czech.Chem.Comm. 19, 885 (1954).

Tetrahedron Letters, No. 21, pp. 749-751, 1961. Pergamon Press Ltd. Printed in Great Britain.

THE HYDROLYTIC CLEAVAGE OF α-ACYLOXY AZOXY COMPOUNDS

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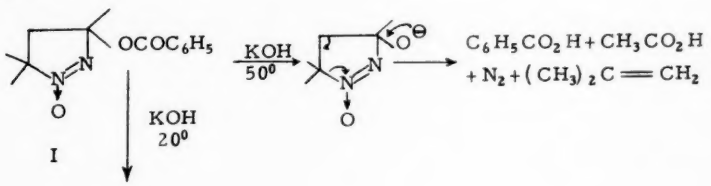
(Received 9 October 1961)

AN interesting and structurally specific hydrolytic cleavage of a pair of α-acyloxy azoxy compounds has been observed. Treatment of 3-benzoyloxy-3,5,5-trimethyl-Δ^1-pyrazoline 1-oxide (I) with 10% ethanolic potassium hydroxide at 50° produced equimolar quantities of benzoic acid, nitrogen, and isobutylene; based on the cleavage scheme (a), acetic acid is presumed to be the other product. This cleavage accounts for about 70% of the starting material. A second concurrent reaction which is favored at lower temperatures produces 3,5,5-trimethylisopyrazole 1-oxide (II).[2]

(a)



I

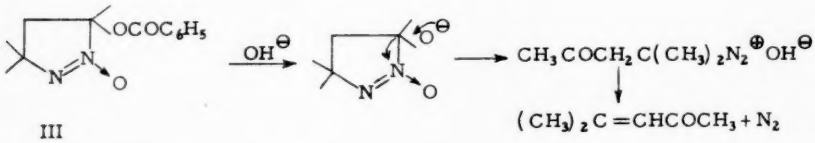
II

[1] This research was carried out under Army Ordnance Contract D-01-021-ORD-11878.

1961

Treatment of 3-benzoyloxy-3,5,5-trimethyl-Δ^1-pyrazoline 2-oxide (III) with ethanolic potassium hydroxide at 50° produced benzoic acid, nitrogen, and mesityl oxide (b).

(b)



III

The direction of cleavage (path a versus path b) of the alkoxide ion produced on hydrolysis is thus controlled by its position in relation to the quaternary nitrogen of the azoxy group. This reaction may be of use in determining the position of the oxygen in saturated aliphatic azoxy compounds, a particularly difficult problem.[4]

The cleavage of I is another example of the fragmentation reactions discussed by Grob[5] and is similar to the fragmentation of γ-hydroxypropylammonium salts recently reported.[6] The cleavage of III is the first well-documented example of a reaction which has been suggested to account for the decomposition products of α-hydroxy azoxy compounds.[7]

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[2] The characterization of II is completely described in a forthcoming publication. Its structure is based on its elementary analysis, infra-red and NMR spectrum, and absorption at 305 mμ in the ultraviolet indicating an extended rather than crossed conjugated system. Unsaturated azoxy compounds of the alternate configuration absorb at 240 mμ.[3]

[3] C.L. Stevens, B.T. Gillis, J.C. French and T.H. Haskell, J.Amer. Chem.Soc. 80, 6088 (1958).

[4] See B. Witkop and H.M. Kissman, J.Amer.Chem.Soc. 75, 1975 (1953) for a discussion of this point.

[5] C.A. Grob, Kekule Symposium on Theoretical Organic Chemistry p. 114. Butterworths, London (1959).

[6] V.J. Traynelis and J.G. Dadura, J.Org.Chem. 26, 686 (1961).

[7] G.M. Robinson and R. Robinson, J.Chem.Soc. 125 834 (1924); B.W. Langley, B. Lythgoe and N.V. Riggs, Ibid. 2309 (1951).

Compounds I and III were obtained from a common intermediate, 3-benzoyloxy-3,5,5-trimethyl-Δ^1-pyrazoline (IV) m.p. 70-71° (aq. ethanol) (Found: N, 11.9 $C_{13}H_{16}N_2O_2$ requires: N, 12.1%) prepared by the action of lead tetrabenzoate on 3,5,5-trimethylpyrazoline.[8] Interestingly enough oxidation with peracetic acid gave exclusively III, m.p. 147-148°, (hexane), (Found: C, 63.0; H, 6.7 $C_{13}H_{16}N_2O_3$ requires: C, 62.9, H, 6.5%) while oxidation with perbenzoic acid gave predominantly I along with small amounts of III. The structure of I, m.p. 89-90° (hexane), is based on its conversion to the known isopyrazole oxide II;[2] the structure of III is based on its being isomeric with I and on the similarity of their infra-red and NMR spectra. Compound I could be prepared directly from 3,5,5-trimethylpyrazoline by treatment with perbenzoic acid.[2]

The corresponding acetates appear to give the same reaction. Further details concerning the characterization of these compounds including rather striking NMR effects and other reactions will be forthcoming.

[8] D.C. Iffland, L. Salisbury and W R. Schafer, J.Amer.Chem.Soc. 83, 747 (1961).

Tetrahedron Letters No. 21, pp. 752-757, 1961. Pergamon Press Ltd. Printed in Great Britain.

THE FORMATION OF A NITRENE INTERMEDIATE IN THE REACTION OF NITRO COMPOUNDS WITH FERROUS OXALATE

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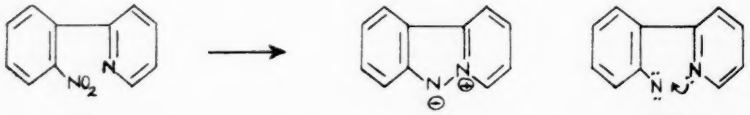
THE reaction of ferrous oxalate with certain aromatic nitro-compounds gives rise to a number of interesting cyclization reactions. For example, 2-nitrodiphenyl gives carbazole[1] whereas 2-nitrodiphenyl-amines give rise to phenazines[2]. The cyclization of 2-o-nitrophenyl-pyridine (I) with ferrous oxalate at 300° took place not onto a pyridine nuclear carbon but onto the pyridine nitrogen atom to give pyrido[1,2-b]-indazole (II)[3]. (II) was also obtained in good yield by heating



I II III

2-o-azidophenylpyridine in decalin. The formation of a nitrene intermediate (III) was suggested[3] for the ferrous oxalate reaction, though a

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[1] H. C. Waterman and D. L. Vivian, J. Org. Chem. 14, 289 (1949).

[2] D. L. Vivian, G. Y. Greenberg and J. L. Hartwell, J. Org. Chem. 16, 1 (1951).

[3] R. A. Abramovitch and K. A. H. Adams, Can. J. Chem. in the press.

concerted, or perhaps two-stage, cyclization and nitrogen elimination was also a strong possibility in the azide cyclization. Formation of a nitrene intermediate in the thermal decomposition of azides has been suggested[4, 5]; a concerted mechanism was not eliminated as a possible alternative in some instances. A nitrene $-\ddot{\underset{\cdot\cdot}{N}}$ would be isoelectronic with a carbene and could be either strongly electrophilic (if the valence electrons are paired) or behave as a biradical in the triplet state (both types of behaviour are known for carbenes which can either add to olefinic double bonds[6] or abstract aliphatic hydrogen atoms[7]). Arguments in favour of the triplet state for nitrenes from azides have recently been put forward by Smolinsky[8]. Some of his arguments may become untenable in the light of the formation of (III) (but no δ-carboline or primary amine) from the thermal decomposition of 2-o-azidophenylpyridine which, however, is unaffected by ultraviolet light. It is clear that in the ferrous oxalate reaction leading to (II) the nitrene intermediate, if it is formed, must be strongly electrophilic (singlet state) since attack takes place exclusively at the pyridine nitrogen electron pair.

A number of reactions have now been carried out with nitrocompounds and ferrous oxalate to establish whether a nitrene is indeed formed, and if it is, whether it behaves as a singlet electrophilic reagent or as a biradical in the triplet state. It was hoped to trap a

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[4] G. Smolinsky, J. Amer. Chem. Soc. 82, 4717 (1960).

[5] E. Wenkert and B. F. Barnett, J. Amer. Chem. Soc. 82, 4671 (1960).

[6] G. L. Closs and L. E. Closs, J. Amer. Chem. Soc. 81, 4996 (1959).

[7] W. R. Moore, H. R. Ward and R. F. Merritt, J. Amer. Chem. Soc. 83, 2019 (1961).

[8] G. Smolinsky, J. Amer. Chem. Soc. 83, 2489 (1961).

nitrene intermediate by building an olefinic double bond into the nitro-compound. Unfortunately, o-nitrostyrene underwent extensive polymerization on being heated with ferrous oxalate and no product could be isolated from this reaction. The crude product did, however, give a positive Erhlich test for indoles. The reaction of o-nitrocinnamic acid with ferrous oxalate at 270-280° was more successful and indole-2-carboxylic acid as well as indole could be isolated in low yield (ferrous oxalate is known[9] to catalyze decarboxylations). Here again, the formation of a nitrene in the singlet state is indicated.

From the decomposition of 2'-azido-2,4,6-trimethylbiphenyl Smolinsky[4] obtained 8,10-dimethylphenanthridine (IV) as the major product, some amine (V) (arising from hydrogen abstraction from the solvent and the dihydrophenanthridine initially formed) and a small amount of 2,4,9-trimethylcarbazole. The action of ferrous oxalate dihydrate on 2'-nitro-2,4,6-trimethylbiphenyl (VI) at 300° in the absence of a solvent gave (V) (27.4%) and (IV) (22.6%). (V) cannot, therefore, arise from the dihydrophenanthridine exclusively. The possibility that the hydrogens could have been abstracted from the water of hydration of the oxalate by the nitrene intermediate was eliminated by the use of anhydrous ferrous oxalate: the proportion of (V) : (IV) was practically unchanged. Hydrogen abstraction by the nitrene must, therefore, be taking place from methyl groups in another molecule (alot of intractable tars were formed in most of the reactions reported here and yields were consequently low) somewhat more readily than intramolecularly. This can be rationalized if it is assumed that (i) the reaction is taking place at the surface of the ferrous oxalate (or its decomposition products

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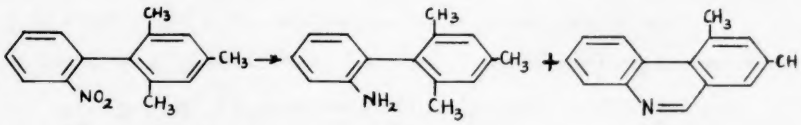
[9] F. Klingstedt, Swensk Papperstidn. 50, 127 (1947).

e.g. FeO), and (ii) that the molecules, the two rings of which are non-coplanar, tend to orient themselves at the oxalate surface such that the nitro group of one molecule may be close in space to the methyl group of another. Some evidence in support of the first assumption was obtained as follows: anhydrous ferrous oxalate was first boiled under reflux with hexadecane (internal temperature 290°); very little decomposition of the ferrous oxalate occurred, even after prolonged heating. On the other hand, when (VI) was added brisk decomposition of the oxalate occurred at about 240°. It therefore seems as though the decomposition of the ferrous oxalate is catalyzed by the nitro-compound adsorbed on its surface and in turn this causes the nitrene to be formed. When a solution of (VI) in hexadecane was heated with anhydrous ferrous oxalate (V) (42.1%) and (IV) (14.8%) were obtained. No other products could be identified or isolated. In this case, hydrogen abstraction from the solvent is also possible.



o-Nitrophenylcyclohexane was heated with anhydrous ferrous oxalate and gave o-aminophenylcyclohexane (51.7%) and carbazole (40%). This reaction and probably also the previous one, undoubtedly involves a nitrene in the triplet state. The formation of carbazole rather than its tetrahydro-derivatives[8] is ascribed to the vigorous conditions of the reaction which can easily lead to dehydrogenation. On the other hand, heating o-nitroethylbenzene (VII) with anhydrous ferrous oxalate gave cis-o-ethylazobenzene (VIII) (15.6%) (comparison of UV and IR with

authentic[10] trans-isomer) together with o-aminoethylbenzene (IX) (4.5%). A very small amount of an amine with a boiling point close to (IX) was detected by gas chromatography. This was not indoline and could perhaps be the benzazetine, arising through hydrogen abstraction from the α-CH_2-, followed by radical coupling. A trace of indole was also detected but no indoline. That the cis-azobenzene did not arise through isomerisation of the trans-form was shown by heating the latter with anhydrous ferrous oxalate. Mainly unchanged trans-o-ethylazobenzene was recovered, together with a trace of amine (IX) and a small amount of a colourless base, b.p. 144-146°/0.5 mm. Formation of the cis-azo-compound is interesting in that it confirms that the molecules tend to be oriented in a preferred fashion on the oxalate surface. Formation of an azo-compound is not unprecedented; 2,2'-dinitrobiphenyl gives 3,4-benzocinnoline[1] and 2-nitrodiphenylsulphide gives 2,2'-bis(phenylmercapto)azobenzene[11] on being heated with ferrous oxalate.

Finally, the action of ferrous oxalate upon a hot solution of nitrobenzene and 1-hexadecene in hexadecane was examined. A small amount of basic material was isolated and distilled to give a fraction b.p. 83-120°/0.17 mm. consisting mainly of aniline (vapour phase chromatography) and a fraction b.p. 180°/0.11 mm. The latter was shown to be homogeneous by chromatography and analyzed for $C_{22}H_{37}N$. Its infrared spectrum showed bands at 3420 cm^{-1} (-NH-) and 970 cm^{-1} (trans--CH= CH-) but no $-CH=CH_2$ band. It took up 1 mole of H_2 on catalytic hydrogenation (no band at 970 cm^{-1}). Structure (X) is suggested for this amine and would arise from a triplet nitrene as follows:

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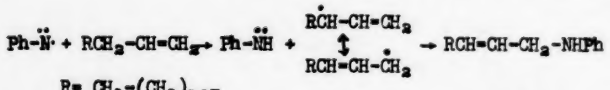
[10] E. Schultz, Ber., 17, 463 (1884).

[11] D. L. Vivian and H. C. Waterman, J. Org. Chem., 21, 914 (1956).



R= $CH_3-(CH_2)_{12}-$

(I)

It would seem, therefore, as though the nitrene intermediate could either behave as a triplet biradical or as a singlet electrophilic reagent; it is probably generated in the triplet state, but could quickly undergo triplet to singlet transition at the surface of the strongly paramagnetic ion.

This work was carried out with the financial support of the National Research Council of Canada which is gratefully acknowledged.

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1961

THE TRIAZENE METHOD FOR THE DEAMINATION OF ALIPHATIC AMINES

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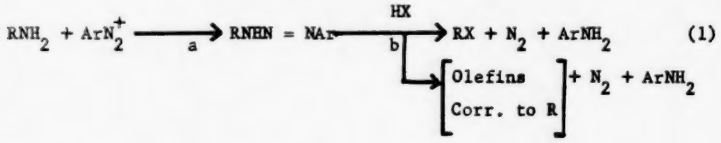
(Received 2 November 1961)

TWO general methods for the deamination of primary aliphatic amines, the nitrous acid-amine reaction[1] and the nitrosoamide decomposition,[2] have been reported in the chemical literature. We would like to call attention to a third method which we have found to be useful for the conversion of primary amines into esters, alkyl halides, ethers, and related derivatives. This method, suggested by work on the reaction of nitrosyl chloride with aliphatic amines,[3] involves triazene intermediates as outlined in equation (1).



(1)

[1] C.R. Noller, Chemistry of Organic Compounds (2nd Ed.) p. 238. W.B. Saunders Philadelphia (1957); A. Streitweiser, Jr., J.Org.Chem. 22, 861 (1957).

[2] Emil H. White, J.Amer.Chem.Soc. 77, 6011 (1955); R. Huisgen and C. Rüchardt, Leibigs Ann. 601, 21 (1956).

[3] Unpublished work by Dr. Bernard E. Weller. Isolated examples of steps a and b (equation 1) have been reported before (footnotes 4 and 5), but the sequence has not been examined previously as a method for the deamination of amines.

The yields for step a[4] in dimethylformamide as the solvent are essentially quantitative and the triazenes formed may be used directly in step b[5] (alternatively, the triazenes may be isolated and purified for use in the nitrogen elimination step). The overall yields for the deamination (Table 1) are superior to those reported for the nitrous acid deamination of amines and about equal to those reported for the nitrosoamide decomposi-

Table 1

Yields for the Triazene Method of Deamination[a]

$$RNH_2 \rightarrow RNHN = NC_6H_4R' \rightarrow RX + N_2 + R'C_6H_4NH_2$$ [b]

Run	R	Acid HX	Solvent (step b)	%RX	% Olefin	$\%R'C_6H_4NH_2$
1[c]	Methyl	3,5DNB[d]	Ether	95	-	-
2	n-Butyl	3,5DNB[d] or HBr	Ether	63	-	-
3	Isobutyl	3,5DNB[d]	Ether	56	-	86
4	Cyclohexyl	Acetic	CH_2Cl_2	38	30	65[e]
5	1-Phenyl-ethyl	Acetic	Hexane	44	28	48[e]
6			CH_3OH	40[f]	-	-

[a] Ave Yields for the two steps, determined for recrystallized or distilled products, and based on the amine (except Run 1 based on triazene).

[b] R' = p-Cl for Run 2 and p-CH_3 for the others.

[c] We thank Mr. Anthony Baum for carrying out this run.

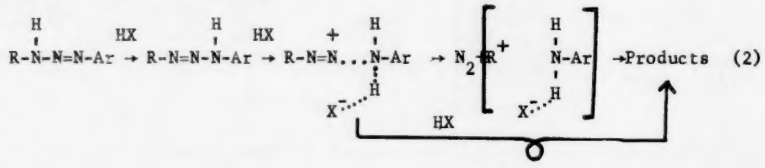
[d] 3,5-Dinitrobenzoic acid.

[e] Secondary amines ($RNHC_6H_4R'$) were isolated from these runs, 16% in run 4 and 25% in run 5.

[f] Little acetate was formed; the value in this case pertains to the solvolysis product $ROCH_3$ (formed with predominant inversion of configuration).

tion.[1,2] Negligible skeletal isomerization occurs in non-polar solvents; in run 2 no detectable s-butyl ester was formed, and in run 3, less than 2% of the iso- and t-butyl isomers was formed. The principle side reactions lead to olefins (equation 1) and to secondary amines. The latter compounds are formed, however, only in the deamination of secondary carbinamines; in run 4, 16% of N-cyclohexyl-p-toluidine was formed, and in run 5, 25% of N-(1-phenylethyl)-toluidine (optically active). These byproducts are in general easily removed from the main product.

The triazene method of deamination leads to considerable apparent racemization; the reaction of 1-(1-phenylethyl)-3-(4 methylphenyl)-triazene with acetic acid gave 1-phenylethyl acetate containing 54% of the enantiomer corresponding to retention of configuration in hexane (run 5), 55% of that form in ether, and 57% in acetic acid. These results and the reaction characteristics cited above can be accounted for by a mechanism related to that proposed for the nitrosoamide decomposition.[6]



In addition to their role as intermediates in the deamination reaction, the triazenes show considerable promise as alkylating agents. Methyl esters

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[4] The method of Goldschmidt [Ber.Dtsch.Chem.Ges. 21, 1016 (1888)] and Dimroth [Ber.Dtsch.Chem.Ges. 38, 670 (1905)], namely the reaction of amines with aqueous solutions of diazonium salts, leads to reasonable triazene yields only if simple, water soluble amines are employed. In Dimroth's later work and in recent work reported in the literature, the alkaryltriazenes used were prepared by the reaction of an aryl azide with an alkyl Grignard reagent.

[5] Goldschmidt[4] was the first to report the acid decomposition of alkaryltriazenes. Dimroth subsequently isolated esters from the reaction of 1-methyl-3-phenyltriazene with a number of acids, and recent Russian work[7b] has extended this to a study of the reaction of benzoic acid with a number of n-alkylnaphthyltriazenes (synthesized from naphthyl azide).

of carboxylic acids can be prepared in high yield with N-methyltriazenes (run 1), and the ease of handling these stable, crystalline compounds (e.g. p-$CH_3C_6H_6N{=}NNHCH_3$, m.p. 82°) recommends them for use as substitutes for diazomethane and for the higher diazoalkanes. The triazenes have also been used (with aluminium alcoholate catalysts) to alkylate certain alcohols, phenols, and mercaptans.[7]

Experimental

A solution of p-chlorobenzenediazonium hexafluorophosphate[8] (recrystallized from acetone-methanol) (2.87 g, 10.1 mmoles) in dimethylformamide (dimethylamine-free) was added slowly to a stirred mixture of n-butylamine (0.73 g, 10.0 mmoles), powdered sodium carbonate (15 g), and dimethylformamide (30 ml) stirred and maintained at -5°. The diazonium salt solution may be used at room temperature; however, a purer product is usually obtained if the diazonium salt solution is prepared in and delivered from a cooled separatory funnel maintained at ca. -50°. The mixture was warmed to 0° and stirred until a negative test was obtained with 2-naphthol (only a few minutes are usually required). Ether was added, the mixture was filtered, and the filtrate was washed thoroughly with water, then dried. (The triazene may be isolated at this point and recrystallized from pentane at low temperatures.[9] The triazene in run 2 melted at 40°, that in run 3 at 19°, and that in run 5 at 39°.)

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[6] Emil H. White and Carl Aufdermarsh, Jr., J.Amer.Chem.Soc. 83, 1179 (1961).

[7a] V.Y. Pochinok and L.P. Limarenko, Ukrain.Khim.Zh. 21, 496, 628 (1955); [b] V.Y. Pochinok and V.A. Portayagina, Ibid. 18, 631 (1952).

[8] Ozark-Mahoning Co., 310 W. 6th St., Tulsa 19, Oklahoma.

[9] Small amounts of 1,1-dimethyl-3-aryltriazene, 1,3-diaryltriazene, and 3-alkyl-1,5-diarylpentazdiene represent the principle impurities in the crude triazene.

A solution (or less satisfactorily a suspension) of 3,5-dinitrobenzoic acid (4.24 g, 20.0 mmoles) in ether was added to the crude triazene and the solution was kept at 25° until nitrogen evolution had ceased (ca. 1-2 hr). (The nitrogen evolution is instantaneous with HBr whereas the reaction with acetic acid requires ca. 12 hr for completion; the reaction is considerably faster in hydrocarbon solvents.) The solution was washed with dilute acid and dilute base, dried, and then evaporated to yield butyl 3,5-dinitrobenzoate, m.p. 61-62° (1.96 g, 73%) tinted with a small amount of a colored impurity. The infra-red spectrum in CCl_4 was superimposable on that of pure n-butyl 3,5-dinitrobenzoate. Recrystallization from hexane yielded in the first crop, 1.69 g (63% yield) of the ester, m.p. 63-64° (lit.[10] 64-64.5°).

Similar results were obtained with p-tolydiazonium fluoborate as the coupling agent, but the products (RX) were less pure.

Methyl triazenes (for alkylations) can be readily prepared by the addition of aqueous solutions of diazonium salts raised to a pH of 7 (Na_2CO_3) to an excess of methylamine at 0°. The product is sublimed and recrystallized.

This work was supported by the Office of Ordnance Research, U.S. Army.

[10] Emil H. White, J.Amer.Chem.Soc. 77, 6081 (1955).

Tetrahedron Letters No. 21, pp. 763-767, 1961. Pergamon Press Ltd. Printed in Great Britain.

CONSTITUTION AND BIOGENESIS OF TWO NEW SESQUITERPENES

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(Received 14 November 1961)

STRUCTURAL investigations of the two new sesquiterpenes (I and II) have provided further examples of optically inactive natural products containing asymmetric centres. The previously described geijerene[1,2] (III) also belongs to this class which requires in the biogenetic scheme, a special step leading to the formation of a racemic product.

We have isolated from gurjun balsam oil and from Dysoxylon frazeranum oil[3] a new sesquiterpene, (δ-elemene), $C_{15}H_{24}$*, b.p.$_{10}$ 107°, n_D^{25} 1.4828, d_4^{25} .8590, $[\alpha]_D \pm 0.0°$ (single peak on Apiezon M at 170°), which yields a crystalline nitrosochloride, m.p. 200°, $[\alpha]_D \pm 0.0°$. The infra-red and ultra-violet spectra are consistent with isolated vinyl (907, 1001 cm^{-1}) and vinylidene (894 cm^{-1}) groups and a trisubstituted double bond (818 cm^{-1}). Complete hydrogenation yields $C_{15}H_{30}$, n_D^{25} 1.4609, d_4^{25} .8399, $[\alpha]_D$ -0.17°, the infra-red spectrum of which leads to a presumption of identity with elemene[4] (IV).

Ozonolysis of δ-elemene followed by treatment of the ozonide with

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* Analyses consistent with quoted formulae were obtained in all cases.

1 M.D. Sutherland, Chem. & Ind. 1220 (1959).

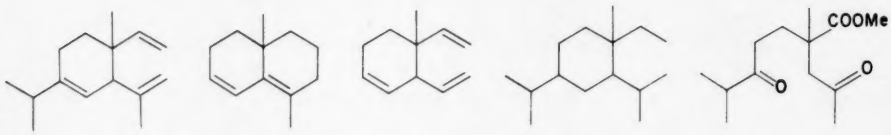
2 A.J. Birch, J. Grimshaw, A.R. Penfold, N. Sheppard and R.N. Speake, J.Chem.Soc. 2286 (1961).

3 R.P. Hildebrand and M.D. Sutherland, Aust.J.Chem. 12, 678 (1959).

4 V. Sykora, J. Cerny, V. Herout and F. Sorm, Coll.Czech.Chem.Comm. 19, 566 (1954).

hydrogen peroxide in acetic acid, yielded a mixture of acids, which were fractionated as methyl esters, the major product being a diketoester (V), $C_{13}H_{22}O_4$, b.p.$_5$ 145-148°, bis-2,4-dinitro-phenylhydrazone, $C_{25}H_{30}N_8O_{10}$, m.p. 138.5-139°.

1961



I II III IV V

Hydrogenation with a deactivated Adams' catalyst in ethanol yielded a dihydro compound, $C_{15}H_{26}$, lacking the intense infra-red vinyl bands shown by δ-elemene. Ozonolysis, etc. yielded a diketone, $C_{13}H_{24}O_2$, b.p.$_5$ 122-127°, $[\alpha]_D$-1.15°, bis-dinitrophenylhydrazone, $C_{25}H_{32}N_8O_8$, m.p. 167°. Hydrogenation with palladized charcoal in ethanol gave a mixture of two tetrahydro compounds, the major product still showing a strong band at 885 cm^{-1} due to a vinylidene group. Oxidation yielded a ketone, (92% purity by gas chromatography), $C_{14}H_{26}O$, $[\alpha]_D$-1.82° (10 cm, hom.), dinitrophenylhydrazone, $C_{20}H_{30}N_4O_4$, m.p. 124-125°.

δ-Elemene was isomerized with either potassamide in liquid ammonia or potassium hydroxide[5] in methanol at 170°, to yield a conjugated hydrocarbon (ε 26,000 at λ_{max} 249 m).

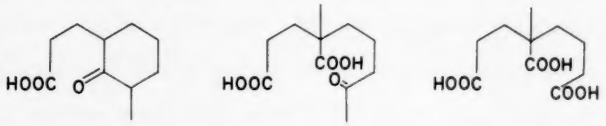
These and other results are compatible only with I, which is entirely consistent with the NMR spectrum.[6] Hence δ-elemene is an isopropyl geijerene and like geijerene[1,2], it is optically inactive although containing two asymmetric centres. The small rotations recorded for non-crystalline products noted above are attributed to the presence of optically active

[5] L. Bateman, J.I. Cunneen and E.S. Waight, J.Chem.Soc. 1714 (1952).

[6] Our thanks are due to Dr. N. Sheppard, University Chemical Laboratory, Cambridge for the measurement and interpretation of the NMR spectrum.

impurities (observable by gas chromatography and optical rotation) in the less pure δ-elemene used for degradation.

The second hydrocarbon (cogeijerene, II) $C_{12}H_{18}$, b.p.$_{10}$ 97°, n_4^{25} 1.5298, d_4^{25} 0.9396, $[\alpha]_D$+0.70°, (single peak with slight shoulder on Apiezon M at 170°), co-occurs with geijerene in the essential oil[7] of Geijera parviflora.



VI VII VIII

Prominent spectral features include a maximum (ε 14,500) at 242 mμ, shoulders at 235 and 251 mμ and a strong infra-red band at 745 cm^{-1}. The Kuhn-Roth isopropylidene estimation yielded no acetone and the C-methyl estimation 1.01 moles of acetic acid. Hydrogenation, peracid titration and molecular refraction indicated two double bonds and two rings. Dehydrogenation over palladized charcoal yielded principally 1,4-dimethylazulene with some 1-methyl-, 1,4-dimethyl- and 1,5-dimethyl-naphthalene indicated by gas chromatography. Reduction with sodium and methanol in liquid ammonia yielded a dihydro compound $C_{12}H_{20}$, b.p.$_{10}$ 91°, d_4^{25} 0.9086, n_4^{25} 1.4962, $[\alpha]_D$±0.0° with a strong band at 800 cm^{-1} instead of that at 745 cm^{-1}.

Ozonolysis, etc. of dihydrocogeijerene yielded two isomeric acids (for one, p-bromophenacyl ester, $C_{20}H_{25}O_4Br$, m.p. 125°), the methyl esters, $C_{13}H_{22}O_3$ (VI), $[\alpha]_D$±0.0°, of which were separated by gas chromatography. Both esters showed carbonyl absorption at 1735 and 1704 cm^{-1} indicative of a heavily substituted cyclohexanone[8]. Ozonolysis etc. of cogeijerene yielded no neutral products but principally the keto acid, VII separated as the

[7] A.R. Penfold, J.Proc.Roy.Soc.N.S.W. 64, 264 (1930).

[8] Y. Mazur and F. Sondheimer, J.Amer.Chem.Soc. 80, 5222 (1958).

dimethyl ester, $C_{13}H_{22}O_5$, b.p.$_5$ 164° $[\alpha]_D \pm 0.0^c$, dinitrophenylhydrazone, $C_{19}H_{26}N_4O_8$, m.p. 80-81°. The acid VII by treatment with alkaline hypobromite, yielded amongst other products bromoform, and the tricarboxylic acid VIII, $C_{10}H_{16}O_6$, m.p. 115°, $[\alpha]_D \pm 0$, tri-p-bromophenacyl ester $C_{34}H_{31}O_9Br_3$, m.p. 127°. An identical tricarboxylic acid was obtained by hypobromite oxidation[9] of β-(1-methyl-2-oxocyclohexyl)-propionic acid[10]. The NMR spectrum[6] of cogeijerene is entirely consistent with its formulation as II. The observed small rotations of liquid products are attributed in this case also, to the presence of optically active impurities in the cogeijerene used for degradations.

While the isolation of certain terpenes (e.g. limonene, α-pinene, δ-cadinene[3]) in approximately racemic form is commonplace, the exactly racemic nature[11] of geijerene ($[\alpha]_D \pm 0.00°$)[12], cogeijerene and δ-elemene requires a special explanation. The postulate of Ruzicka[13] in 1953 and Hendrickson[14] in 1959, that elemol (IX) results from a recyclization of a ten-ring precursor (X) can be reconciled with the optically inactive nature of our terpenoids if it is assumed that the recyclization takes place in the absence of enzymatic control. The elemol and β-elemene[15] precursors would yield optically active products as is observed, since the precursors

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[9] M.W. Farrer, J.Org.Chem. 1708 (1957).

[10] R.L. Frank and R.C. Pierle, J.Amer.Chem.Soc. 73, 724 (1951).

[11] We wish to thank Professor C. Djerassi for measurements of the optical rotatory dispersion curves of these substances. Geijerene and δ-elemene showed zero rotation from 600 to 250 mμ. In the case of cogeijerene, a rotation of approx. -11° at 325 mμ was observed and is attributed to a minor impurity.

[12] W.R. Owen and M.D. Sutherland, J.Sci. Food Agric. 1, 88 (1956).

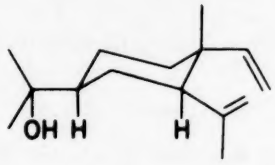
[13] L. Ruzicka, Experientia 9, 357 (1953).

[14] J.B. Hendrickson, Tetrahedron 7, 82 (1959).

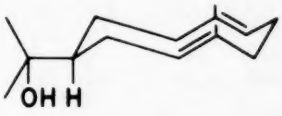
[15] V. Sykora, V. Herout and F. Sorm, Coll.Czech.Chem.Comm. 21, 267 (1956).

have already one asymmetric centre. Geijerene and δ-elemene would be inactive since such an asymmetric centre is lacking in the appropriate precursors. The same inactive precursor (XI) of geijerene could also yield optically inactive cogeijerene through non-enzymatic protonation and deprotonation.

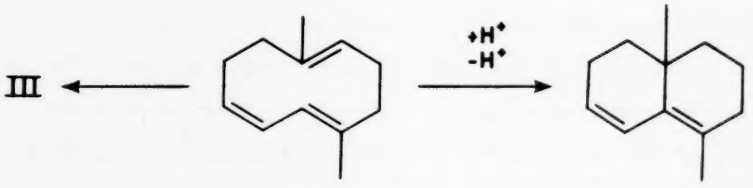
The question as to whether these optically inactive sesquiterpenes are present in the living plant or result from the isolation procedures[16] is under investigation.



IX



X



XI II

[16] Y-R. Naves, Bull.Soc.Chim.Fr. 1518 (1960).

Tetrahedron Letters No. 21, pp. 768-770, 1961. Pergamon Press Ltd. Printed in Great Britain.

THE OCCURRENCE OF PHYTANE IN PETROLEUM

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Research Centre

Petroleum Division

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(Received 13 October 1961; in revised form 3 November 1961)

IN the course of recent studies on the composition of petroleum, we had occasion to remove normal paraffins from petroleum distillates boiling in the range 250°-370°C by means of molecular sieve 5A. The gas liquid chromatogram obtained on a non-aromatic fraction of an Agha Jari (Iran) distillate from which normal paraffins had been removed, showed very strong peaks having retention volumes on a silicone column very close to those of n-heptadecane and n-octadecane. These peaks were superimposed on the "envelope" which is present in chromatograms of all petroleum distillate fractions boiling above about 200°C, and it was estimated from their areas that the compounds giving rise to them were present, very approximately, to the extent of 0.3 per cent weight of the crude oil. No peaks of comparable magnitude were present at the retention volumes of other n-paraffins (C_{16} and C_{19} to C_{23}). This suggested that these two compounds did not, unlike many components of petroleum, belong to a series in which adjacent members, differing by one carbon atom, are present to approximately the same extent, e.g. the n- and 2-methyl-alkanes.

Our initial postulate was that they were both C_{20} compounds based on isoprene and to substantiate this they were isolated (5 mg of each) using a combination of fractional distillation, liquid thermal diffusion and trapping from gas chromatographic columns using a polyphenyl ether and silicone oil as successive stationary phases. The higher boiling of the two compounds had an infra-red spectrum very similar to that of phytane (2:6:10:14-tetramethylhexadecane, n_D^{20} 1.4418, synthesized from commercial phytol by catalytic hydrogenation with a platinum catalyst at 20°C and 100 atm, conversion of the dihydrophytol to its p-toluene-sulphonate, and reduction of this with lithium aluminium hydride) which in turn was identical within the limits of reproducibility with that recorded by Pliva and Sörensen[1]. Differences in the spectra of the isolated and synthetic compounds were the presence of minor peaks at 8.22, 10.1, 10.98 and 11.26μ and an overall higher absorbance in the former. Mass spectra of the isolated and synthetic materials were also similar, differences being attributable to the presence of other C_{20} branched chain paraffins. These results coupled with the identity of retention volumes (isolated and synthetic respectively: 1.06, 1.06 relative to n-octadecane with silicone oil as stationary phase at 257°C; 0.89, 0.89 relative to n-octadecane with a C_{30} polyphenyl ether as stationary phase at 257°C) make it reasonably certain that the compound almost coincident with n-octadecane on the silicone column is phytane.

The mass spectrum of the material almost coincident with n-heptadecane was, however, that of a C_{19} isoparaffin, not that of a hydrogenated isoprene tetramer. Identity of its retention volumes (0.79 on silicone, 0.65 on polyphenyl ether, conditions as above) with those of 2:6:10:14-tetra-

[1] J. Pliva and N.A. Sörensen, Acta Chem.Scand. 4, 846 (1950).

methylpentadecane[2] (0.79 and 0.64 respectively) suggests that it may have this structure. The quantity of the two hydrocarbons isolated was insufficient to permit the determination of their optical activity, however, a determination on a phytane-containing concentrate showed no measurable activity. Further confirmation of the structures of the two compounds, data on the amount present in a number of different crude oils and a discussion of the significance of their presence in petroleum (cf. page 312 of ref. 3) will form the subject of a future communication.

Acknowledgement - Our thanks are due to the Chairman and Directors of The British Petroleum Company Limited for permission to publish these results.

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[2] J.S. Sörensen and N.A. Sörensen, Acta Chem.Scand. 3, 939 (1949).

[3] S.F. Birch, T.V. Cullum, R.A. Dean and D.G. Redford, Tetrahedron 7, 311 (1959).

Tetrahedron Letters No. 21, pp. 771-774, 1961. Pergamon Press Ltd. Printed in Great Britain.

THE DESCRIPTION OF THE EXCITED STATES OF AROMATIC MOLECULES CONTAINING MESOMERIC SUBSTITUENTS

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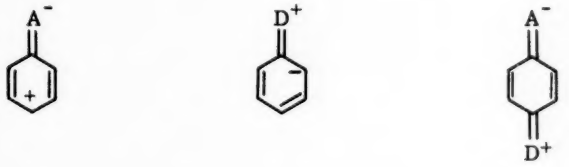
M. Godfrey and J. N. Murrell, Dept. of Chemistry, The University, Sheffield.

(Received 14 November 1961)

IT has become established to formulate the excited states of aromatic molecules containing mesomeric groups by means of resonance structures of the following type:



A and D are respectively electron accepting (-M) and electron donating (+M) groups.

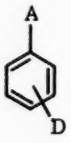
If this formulation is adopted, it leads to certain conclusions concerning the relative energies and the charge distributions of these excited states. In this way it is possible to understand general properties such as the bathochromic shift of the absorption spectrum of an aromatic nucleus on substitution with either an A or a D, and the fact that molecules containing donor groups, for example ArOH, ArNHR, $ArNR_2H^+$ and ArSH, are stronger acids in the first excited states than in the ground states whereas those containing acceptor groups for example ArCOOH, $ArCR{=}OH^+$ and $ArCR{=}NRH^+$ become weaker acids in the excited states. [1]

1 A. Weller, Progress in Reaction Kinetics 1, 187 (1961).

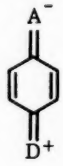
On the other hand, it should be emphasised that the resonance theory fails badly when called upon to predict more detailed results such as the relative excitation energies of polysubstituted aromatic systems and the detailed excited state electron distribution in the aromatic fragment. However these detailed results, as well as the general results, can readily be understood on the basis of a molecular orbital model incorporating locally excited and charge transfer states.

Example 1.

The spectra of the ortho and meta isomers of molecules of the type I are quite similar to each other but different from those of the para isomers. Also the former generally absorb at longer wavelengths than the latter.



I



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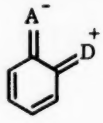
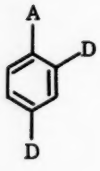


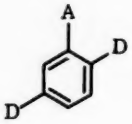
III

This cannot be understood on the basis of resonance theory which would lead one to expect that the meta compounds should be the odd ones out, as no structures of the type II or III can be drawn for them.

Likewise, in polysubstituted molecules such as IV to VII, those with the donating groups in para relationship absorb at the longest wavelength, even though fewer polar resonance structures without long bonds can be drawn for them.



IV



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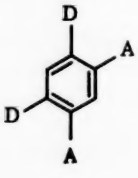

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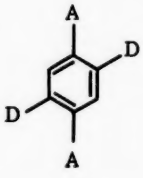
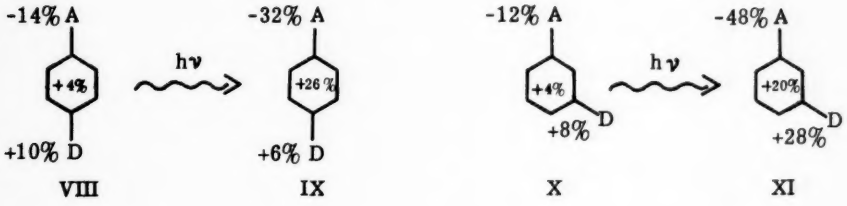


VII

The molecular orbital theory however is in agreement with all the above experimental results.

Example 2.

Zimmerman[2] has reported that a solution of meta-nitrophenyl-tritylether in aqueous dioxane, though almost completely unreactive in the dark, hydrolyses rapidly when irradiated. The para isomer however, which reacts in the dark, hydrolyses only a little faster on irradiation. Similar results have been obtained by Havinga[3] on the photochemical hydrolysis of meta and para-nitrophenyl-phosphates. These results which are diametrically opposed to the resonance expectation are again easily explained by the above molecular orbital model. In formulae VIII to XI the change in electron density on going from the ground to the excited state is given for a typical model (electron affinity E_A = -1 ev, ionisation potential I_D = 10 ev).



VIII IX X XI

Example 3.

An estimate of the change, on excitation, of the charge density at a particular atom in an aromatic system may be obtained from the effect of introducing a more electronegative atom at that position. The absorption spectra of 2- and 3-nitropyridines are similar to each other and different

2 H. Zimmerman, Chem. and Eng. News July 17, 1961, p.46.

3 E. Havinga, R. O. De Jongh and W. Dorst, Rec. Trav. Chim. 75, 378 (1956); E. Havinga, Koninkl. Nederl. Akad. Wetenschappen 70, 52 (1961), and personal communication.

from that of 4-nitropyridine.[4] The same is true for the aminopyridines.[5] The spectral shifts which occur on the protonation of an amino-aza-compound are also contrary to the resonance picture. For example the red shift of the first bands of 6- and 7-aminoquinolines on protonation are approximately equal.[6] Again these results are to be expected on the basis of a molecular orbital model.

A detailed theorectical treatment of the excited states of these compounds will be published by us in the near future.

Acknowledgements - R. Grinter and E. Heilbronner thank the CIBA Aktiengesellschaft and the Schweizerische Nationalfonds (Projekt Nr. 1918) for supporting this work.

4 W. Gruber, Canad. J. Chem. 31, 1020 (1953).
5 E. A. Steck and G. W. Ewing, J.A.C.S. 70, 3397 (1948).
6 J. N. Murrell, J. Chem. Soc. 296 (1959).

Tetrahedron Letters No. 21, pp. 775-776, 1961. Pergamon Press Ltd. Printed in Great Britain.

THE PREPARATION OF SILVER FLUOROBORATE: A WARNING

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(Received 6 November 1961)

IN connection with a preparation of silver fluoroborate by the method of Meerwein[1] we have experienced an explosion of great violence. A mixture of silver oxide and boron trifluoride etherate was heated in nitromethane, and the residue containing silver metaborate and unreacted silver oxide was then removed by filtration using a sintered glass funnel. This dark residue was washed with water and then allowed to stand for several days. At the end of this interval more water was added and the funnel swirled to loosen the solid so it could be discarded. Without warning the residue detonated with terrific brisance.

The ease with which the solid detonated suggested that it might have contained silver fulminate. This conjecture is strongly supported by Nef's observation that treatment of an ice-cold aqueous solution of the sodium salt of nitromethane with mercuric chloride causes precipitation of mercuric fulminate.[2] A silver analog of this transformation is not unlikely in a reaction mixture containing both nitromethane and silver oxide.

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[1] H. Meerwein, V. Hederich, and K. Wunderlich, Arch.Pharm. 291, 541 541 (1958).

[2] N.V. Sidgwick, The Organic Chemistry of Nitrogen p. 339. Oxford University Press (1937). We are indebted to Mr. R. Lawton for bringing this reference to our attention.

We strongly recommend Olah's method for preparing silver fluoroborate, which employs argentous fluoride instead of the oxide.[3]

[3] G.A. Olah and H.W. Quinn, J.Inorg.Nucl.Chem. 14, 295 (1960).

1961

Tetrahedron Letters No. 21, pp. 777-780, 1961. Pergamon Press Ltd. Printed in Great Britain.

SYNTHESIS OF A NITROGEN-FREE DERIVATIVE OF JERVINE

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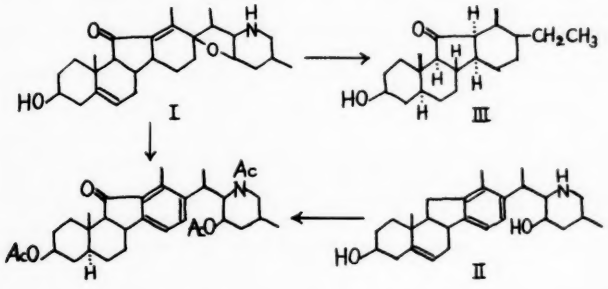
Sapporo, Japan

(Received 10 October 1961; in revised form 13 November 1961)

The veratrum alkaloids, jervine (I) and veratramine (II) possess the C-nor-D-homosteroid skeleton as determined by Wintersteiner and co-workers.[1] Recently K. Tsuda, S. Okuda and H. Kataoka have determined the absolute configuration of the methyl group in the piperidine residue,[2] but the correlation of jervine-derived products with derivatives of conventional steroids has been lacking. We have now succeeded in obtaining the degradation product (III) of Fried and Klingsberg[3] in the course of our studies of C-nor-D-homopregnanes derived from hecogenin.



[1] J. Fried, O. Wintersteiner, M. Moore, B. M. Iselin and A. Klingsberg, J. Am. Chem. Soc. 73, 2970 (1951).

[2] K. Tsuda, S. Okuda and H. Kataoka, 14th Annual Meeting of Pharmaceutical Society of Japan (Sapporo, July 19, 1961).

[3] J. Fried and A. Klingsberg, J. Am. Chem. Soc. 75, 4929 (1953).

3β-Hydroxy-12,12-ethylenedioxy-5α-pregnan-20-one (IV)[4] prepared in nine steps from hecogenin was reduced to 3β-hydroxy-12,12-ethylenedioxy-5α-pregnane (V) (m.p. 165°) by Huang-Minlon's method in 87% yield. Removal of the ethylenedioxy group by heating in 90% acetic acid gave 3β-hydroxy-5α-pregnane-12-one (VI) (m.p. 186°, 85% yield), which was converted into the acetate (VII) (m.p. 140°, 90% yield). Bromination of VII in benzene readily afforded 3β-acetoxy-11α-bromo-5α-pregnane-12-one (VIII) (m.p. 148°, 50% yield), which was carefully hydrolyzed to 3β,11β-dihydroxy-5α-pregnane-12-one (IX) (m.p. 192-193°, 50% yield). The p-toluenesulfonylhydrazone of IX, (X) (m.p. 235° decomp.), which was obtained on treatment of IX with p-toluenesulfonylhydrazide in acetic acid, was heated with sodium ethyleneglycolate at 170°,[5] to give XI, m.p. 190°, $[\alpha]_D$+34.0°(C, 0.94 $CHCl_3$), Found: C, 79.25; H, 10.85. Compound XI possesses a double bond exocyclic to a five-membered ring because of its relatively strong absorption at 1678 cm^{-1} and its reduction with PtO_2 or Pd-C to a saturated mono-ol with loss of the 11-hydroxyl group suggesting the presence of an allylic structure. Treatment of XI with acetic anhydride-pyridine afforded a monoacetate (XII), m.p. 152°, $[\alpha]_D$+31.2° (C, 1.09 $CHCl_3$), IR: 3580 (11-hydroxyl), 1738 (3-acetyl), 1678 cm^{-1} (double bond), Found: C, 76.50; H, 10.07, in 65% yield. On mild oxidation with CrO_3 in pyridine the acetate XII produced an α,β-unsaturated ketone (XIII), m.p. 143.5°, $[\alpha]_D$-34.2°(C, 1.35 $CHCl_3$), Found: C, 77.01; H, 9.55, in 70% yield.

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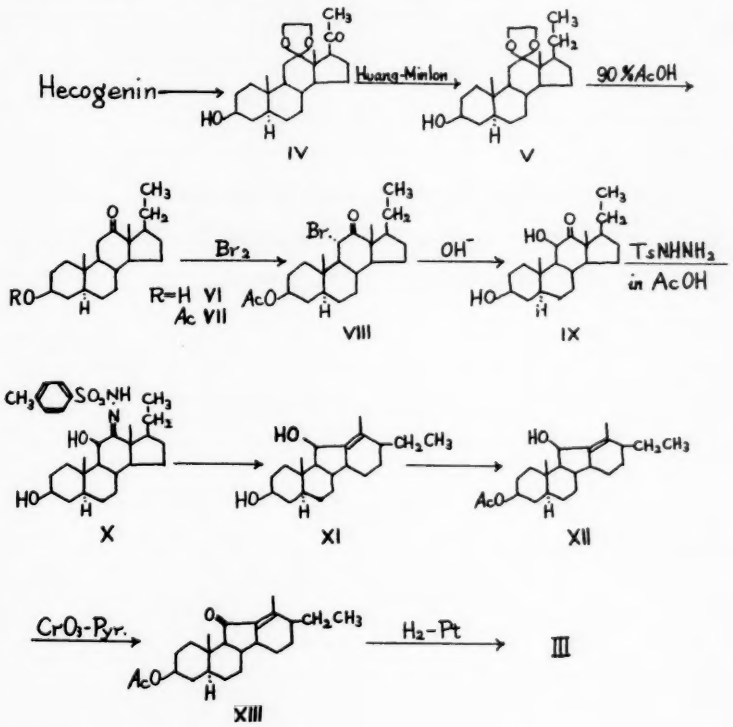
[4] D.N. Kirk, D.K. Patel and V. Petrow, J. Chem. Soc. 1957, 1046.

[5] R. Hirschman, C.S. Snoddy, Jr., C.F. Hiskey and N.L. Wendler, J. Am. Chem. Soc. 75, 4929 (1953).

This substance has the same chromophore as jervine showing a UV maximum at 255 mμ (log ε=4.1), 354 mμ (log ε=1.89) and an IR spectrum closely resembling that of jervine in the carbonyl region.

Catalytic hydrogenation of XIII with PtO_2 gave a dihydro product, m.p. 118.2-118.9°, $[\alpha]_D$-15.5° (C, 1.55 $CHCl_3$), Found: C, 76.95; H, 10.03, which was proved to be identical with III prepared from jervine[3] by mixed melting point[6] and comparison of IR spectra.



6 J. Fried and A. Klingsberg reported the melting point and specific rotation of III as 114-116°, $[\alpha]_D$-8.6°($CHCl_3$), but present sample from jervine shows m.p. 118-119° and $[\alpha]_D$-15.8° ($CHCl_3$).

Since jervine and veratramine have been correlated with each other,[7] the C-nor-D-homo ring system of both compounds has been confirmed conclusively. Moreover, the stereochemistry at 8, 9 and 14 has been shown to be that of conventional steroids.

Acknowledgement: The authors wish to express their thanks to Drs. K. Tsuda, S. Okuda, J. Fried and N. Masamune for their kind donation of III.

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[7] O. Wintersteiner and M. Moore, J. Am. Chem. Soc. 75, 4938 (1953).
Ch. Tamm and O. Wintersteiner, J. Am. Chem. Soc. 74, 3842 (1952).
O. Wintersteiner and N. Kosansky, J. Am. Chem. Soc. 74, 4474 (1952).

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THE STRUCTURE OF HELLER'S DIHYDROQUINOLINE DIMERS

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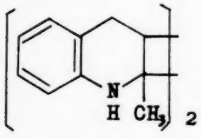
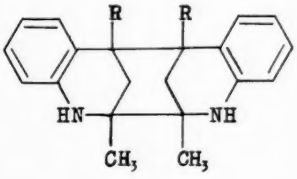
Heller[1] has reported the preparation of a number of methyldihydroquinoline dimers by the reduction of methylquinolines with zinc and acid. These dimers are weakly basic diamines which are unreactive toward most amine reagents, but are readily oxidized to the parent quinolines. Meisenheimer[2] has suggested the formulation I for dihydroquinaldine dimer. This structure, while consistent with the chemical evidence available, seems improbable on mechanistic grounds and has now been found to be incompatible with the n.m.r. spectrum of the dimer.



I



II, R = H

III, R = CH_3

[1] G. Heller and A. Sourlis, Ber. 41, 2692 (1908); G. Heller, ibid. 44, 2106 (1911); 47, 2893 (1914).

Dihydroquinaldine dimer was prepared by a modification of Heller's method with the use of zinc amalgam and hydrochloric acid; the dimer had m.p. 183.5 - 184.0° (lit.[2] 179-180°) after repeated sublimation [Calcd. for $C_{20}H_{22}N_2$: C, 82.72; H, 7.64; N, 9.65: M.W., 290. Found: C, 82.77; H, 7.60; N, 9.70: M.W., 324. (Calcd. for $C_{20}H_{20}N_2$: C, 83.29; H, 6.99; N, 9.71)]. Its infrared spectrum shows the presence of NH (2.95 u) and the absence of ethylenic double bond absorption. Its ultraviolet spectrum in neutral solution [λ_{max}^{EtOH} (ϵ) 251 (16,000), 315 (5500) mμ] resembles that of 1,2,3,4-tetrahydroquinaldine [λ_{max}^{EtOH} (ϵ) 248 (7300), 299 (2000) mμ] insofar as the positions of the bands are concerned and indicates, on the basis of the band intensities, that two such systems are present. In 0.25 M acid solution the spectrum corresponds to that of an equimolar mixture of 1,2,3,4-tetrahydroquinaldine and its hydrochloride, demonstrating the presence of the monoprotonated species. Prolonged treatment of the dimer with boiling acetic anhydride gives a mono-acetyl derivative, m.p. 178.5-182° (Calcd. for $C_{22}H_{24}N_2O$: C, 79.49; H, 7.28; N, 8.43. Found: C, 79.41; H, 7.15; N, 8.19). Potentiometric titration confirms the ultraviolet spectral evidence in that only one amino group is titratable (pK_b 10.5) under the conditions used.[3] This together with the fact that the monoacetyl derivative is a weaker base (pK_b 11.2) than the dimer itself suggests that the two amino groups are close-lying. The ready oxidation of the dimer to quinaldine[1,2] has been confirmed; with silver nitrate in aqueous acetone as oxidant quinaldine is

[2] J. Meisenheimer and E. Stotz, ibid. 58, 2330 (1925).

[3] J.S.Fritz, Anal. Chem. 25, 407 (1953).

formed in 78% yield (based on the formation of two moles from one mole of dimer), demonstrating that the two monomer units retain their skeletal integrity in the dimer.

The n.m.r. spectrum of the dimer is particularly informative. The methyl hydrogen signal (τ=8.82 p.p.m.) is unsplit, thus fixing two of the four termini of the two bonds between the monomer units as 2 and 2'. The remainder of the spectrum consists of the aromatic hydrogen multiplet (τ=2.85-3.63 p.p.m.), the NH hydrogen signal (τ=6.27 p.p.m.), and a complex doublet (τ=7.15 p.p.m.) - quartet (τ=7.93, 8.13,(8.80), 9.00] pattern assignable to two ABX groupings. Although structures of type I contain two ABX groupings, the AB hydrogen atoms are benzylic and their signals would be expected to occur at appreciably lower fields than those observed. The only structure which is consistent with this spectrum and the other data is II, in which the monomer units are joined 2,2' and 4,4'; this possesses two identical ABX groupings, but the AB hydrogen atoms are not benzylic.[4]

Support for the assignment of structure II is forthcoming from the n.m.r. spectrum of the related 2,4-dimethyldihydroquinoline dimer, m.p. 215-216° (lit.[1] m.p.176°), $\lambda_{max}^{CHCl_3}$ 2.95u [Calcd. for $C_{22}H_{26}N_2$: C, 82.97; H, 8.23; N, 8.80; M.W., 318. Found: C, 83.03; H, 8.28; N, 8.68; M.W.330 (Calcd. for $C_{22}H_{24}N_2$: C, 83.50; H, 7.64; N, 8.85)], formed by reduction of 2,4-dimethylquinoline with zinc and hydrochloric acid. This spectrum showed, in addition to the aromatic hydrogen multiplet (τ=2.74 - 3.65 p.p.m.) and NH hydrogen singlet (τ=6.18 p.p.m.), an unsplit methyl hydrogen

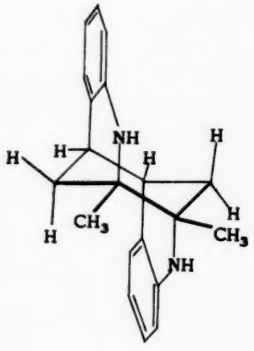
[4] The related structure with the monomer units joined 2,4' and 4,2' is rejected on the basis of the pK_b data.

band (τ=8.80 p.p.m.) attributable to superimposition of signals due to the 2,2',4 and 4' methyl groups, and a simple AB quartet [τ=8.05, 8.28,(8.80), 9.00 p.p.m.]. Its relationship to the n.m.r. spectrum of dihydroquinaldine dimer can readily be interpreted in terms of structure III, analogous to II, but not in terms of structures analogous either to I or to other formulations for dihydroquinaldine dimer.

1961

Although the stereochemistry of dihydroquinaldine dimer has not been rigorously determined, we propose the provisional assignment of structure IV, rather than the other diastereoisomer of II in which the two NH groups are in the cis-relationship with respect to the cyclohexane ring. This assignment appears to be in better accord with the relatively small increase in the pK_b of the dimer which results on monoacetylation, and with the magnitude of the relative chemical shift (δ=0.85 p.p.m.) for the hydrogen atoms of each methylene group. It may be noted that the other diastereoisomer, which requires a boat or twist form of the cyclohexane ring, is subject to severe steric interactions absent in structure IV.

IV



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POLYCYCLIC BASES-III

THE PREPARATION AND STRUCTURE OF A NOVEL SPIROOXAZINE

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(Received 14 November 1961)

DURING the course of a study on the total synthesis of aza-steroids, an unusual ring closure reaction was observed when α-(3-cyclopentenyl)tert-butanol (b.p. 74° (6mm); n_D^{30}, 1.4645) was heated with an excess of acetonitrile in cold concentrated sulfuric acid. The product, 2,4,4-trimethyl-6,6-tetramethylene-5,6-dihydro-1,3-oxazine (I) was formed in 63% yield, b.p., 77-79° (4mm); n_D^{30}, 1.4694; $\lambda_{max}^{CCl_4}$ 6.01 (C=N). Found for $C_{11}H_{19}ON$: C, 73.12; H, 10.34; N, 7.75; picrate (EtOH), 154-155°; hydrobromide (EtOH-EtOAc), 173-175°. The use of α-(1-cyclopentenyl) t-butanol in place of the 3-substituted olefin gave the same product in somewhat lower yield (51%). This novel ring closure represents a further example of the nitrile-tertiary alcohol condensation which has, to date, led to a variety of heterocyclic systems.[1-5]

On the basis of the accumulated data for the preparation of heterocycles via this technique, the mechanism of this oxazine formation may be formulated in the manner described in Fig. 1. It is evident from the reaction scheme

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[1] E.J. Tillmanns and J.J. Ritter, J.Org.Chem. 22, 839 (1957).

[2] A.I. Meyers and J.J. Ritter, J.Org.Chem. 23, 1918 (1958).

[3] A.I. Meyers, J.Org.Chem. 25, 147, 1147, 2133 (1960).

[4] A.I. Meyers and W.Y. Libano, J.Org.Chem. 26, 1682 (1961).

[5] A.I. Meyers and W.Y. Libano, J.Org.Chem. 26. In press. (1961).

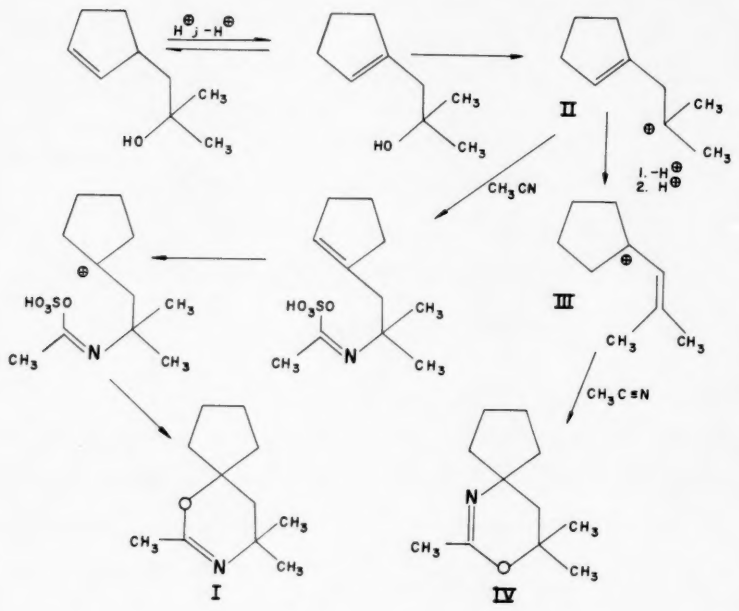

FIG. 1

that the simultaneous formation of the isomeric oxazine (IV) is possible through a rearrangement of the carbonium ion, II, to III. However, only a single product was obtained as indicated by vapor phase chromotography. That I was the product obtained in this reaction was supported by the sequence of reactions described in Fig. 2. Hydrolytic cleavage of the oxazine in 10% sodium hydroxide gave the hydroxyamide (V) as a viscous oil, $\lambda_{max}^{CCl_4}$ 2.76 (-OH), 2.91 (-NH), 5.89 (amide I), 6.61 (amide II). Found for $C_{11}H_2O_2N$: C, 70.12; H, 12.18; N, 7.90. Dehydration with iodine in benzene gave the unsaturated amide (VI) as a mixture of isomers, m.p. 84-92. Found for $C_{11}H_{19}ON$; C, 73.05; H, 10.41; N, 7.70. Reduction of the isomeric amides with rhodium-on-alumina at 3 atmospheres afforded the pure saturated amide (VII), m.p. 74-75°. Found for $C_{11}H_{21}ON$: C, 64.30; H, 11.12; N,

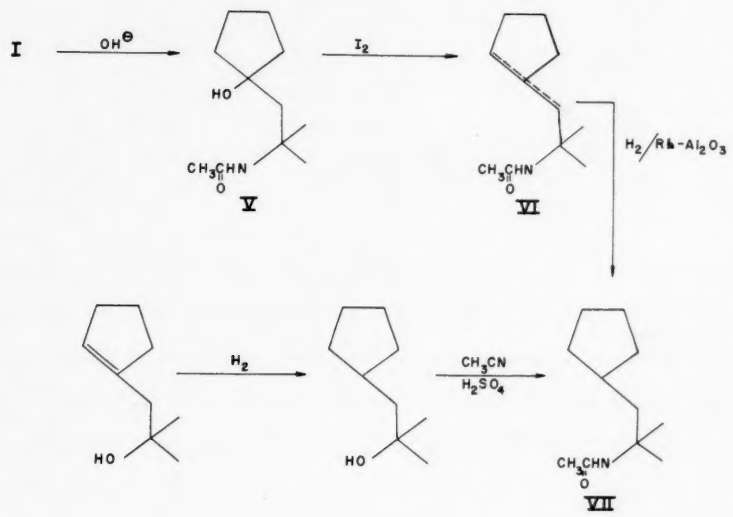

FIG. 2

7.40. This amide was alternately prepared via the Ritter reaction[6] from α-(cyclopentyl) t-butanol (b.p. 59-61 (0.5 mm); n_D^{30}, 1.4536) and acetonitrile in concentrated sulfuric acid. The amides obtained from both routes proved to be identical in every respect.

Although the degradative studies on the oxazine would, a priori, seem to eliminate the possibility of the product possessing structure IV, the results would prove to be inconclusive if a rearrangement occurred during the Ritter reaction preparation of VII through a bridged ion (VIII). The amide resulting from the rearranged carbonium ion (IX) would then support the structural assignment, IV. This possibility is not unlikely in view of the previous observation of a 1,3-hydride shift in norbornyl systems.[7]

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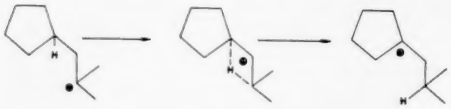
[6] J.J. Ritter and P.P. Minieri, J.Amer.Chem.Soc. 70, 4045, 4048 (1948).

[7] J.D. Roberts, C.C. Lee, and W.H. Saunders, J.Amer.Chem.Soc. 76, 4501 (1954).



VIII IX

FIG. 3

The structure of the oxazine was unambiguously confirmed as a result of a concurrent X-ray crystallographic study on the hydrobromide derivative. The lack of molecular parameters in the literature pertaining to a dihydro-1,3-oxazine system prompted this study by one of the authors (L.M.T.).

Suitable single crystals of the hydrobromide salt of the compound were grown from a solution of ethyl alcohol and ethyl acetate. Three-dimensional data were taken of the salt which was monoclinic, space group $P_{21/c}$ with four molecules per unit cell. The cell dimensions are $a=7.19_8$, $b=12.09_1$, $c=14.57_4$ Å and the monoclinic angle $\beta= 102^{\circ}10'$.

The heavy atom technique was used in determining the positions of the atoms. The bromine position was determined by vector-convergence maps of the three axial projections. The remaining atoms were found by Fourier methods utilizing the phases calculated from the bromine atom position.

The structure was refined isotropically by the least squares method utilizing the full matrix. The behavior of the temperature factors corroborated the differences in peak heights of the two heterocyclic atoms in the electron density maps and thus allowed the nitrogen and oxygen atoms to be unambiguously identified. The reliability index

$$R = \frac{\sum \left| |F_o| - |F_c| \right|}{\sum |F_o|}$$

was 0.118 for all of the observed data and $R_{hko} = 0.120$, $R_{okl} = 0.158$, $R_{hol} = 0.110$ for the three axial projections.

Although further anisotropic refinements (as indicated by the difference electron-density map) are planned, the structure (Ia) is essentially determined. The scope of this ring closure reaction as well as the completed X-ray study will be published separately at a later date.

FIG. 4

Bond distances (Å)	Bond angles
$\overline{C\text{–}O}$ $1.39 \pm .01_0$	$\angle CCC$ $107^\circ 30' + 3^\circ 30'$
$\overline{C\text{–}C}$ $1.56 \pm .04_5$	$\angle COC$ 115°
$\overline{C\text{–}N}$ 1.48_5	$\angle CNO$ 120°
$\overline{C\text{–}N}$ 1.38_7	$\angle CNC$ 121°
$-NH^+ \ldots\ldots Br^-$ 3.24	

The bond lengths and bond angles are tabulated below with their average deviations as indicated. The bond distances and bond angles (except the C=N distance) correlate rather well with the predicted values,[8] with the angles very nicely corroborating the sp^3 hybridization for the carbon atoms

[8] L. Pauling, Nature of the Chemical Bond Cornell University Press (1960).

[9] L. Merritt and E. Lanterman, Acta Cryst. 5, 811 (1952).

[10] B. Penfold, Acta Cryst. 6, 591 (1953).

(107° 30 $\pm$ 3° 30') and the sp^2 hybridization about the nitrogen atom (120° 30' $\pm$ 3°). The C=N distance is quite long at 1.38$_7$ Å as compared to the open chain C=N distance of 1.27 Å in dimethylglyoxime[9] and somewhat longer than the carbon nitrogen distance of 1.33$_5$ Å in a conjugated ring system such as 2-pyridone.[10] No heterocyclic C=N distances in unconjugated systems were found in the literature. Consequently, the anisotropic refinements will be of interest in indicating how statistically significant this variation will be.

Acknowledgement - The authors wish to express their gratitude to the following agencies for financial assistance to support this and subsequent studies: American Cancer Society Summer Fellowship (to J. S.); National Institutes of Health (RG-6248) (to A. I. M.); National Institutes of Health (RG-8348) (to L. M. T.).

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961

STEREOSPECIFIC SYNTHESES OF rac.-N-METHYLRHYNCHOPHYLLANE FOR STEREOCHEMISTRY OF RHYNCHOPHYLLINE

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(Received 20 November 1961)

RHYNCHOPHYLLINE ($C_{22}H_{28}O_4N_2$) is an alkaloid of Uncaria rhynchophylla MIQ. (Ouroparia rhynchophylla MATSUM.), which was first isolated and named by Kondo[1]. In recent years, Marion et al.[2] proposed the formula (I) for rhynchophylline, and Nozoye[3] suggested the partial stereo-formula (IV) for the same alkaloid. This alkaloid in acetic acid readily isomerizes to isorhynchophylline[3,4,2b] which has also been found to occur in nature and has the same plane formula (I).[2b,3] Rhynchophylline is converted with dilute hydrochloric acid into rhynchophyllal (II), and then by the Wolff-Kishner reduction to rhynchophyllane* (III, R=H), which is readily derived to N-methylrhynchophyllane (III, R=CH_3).[2b]

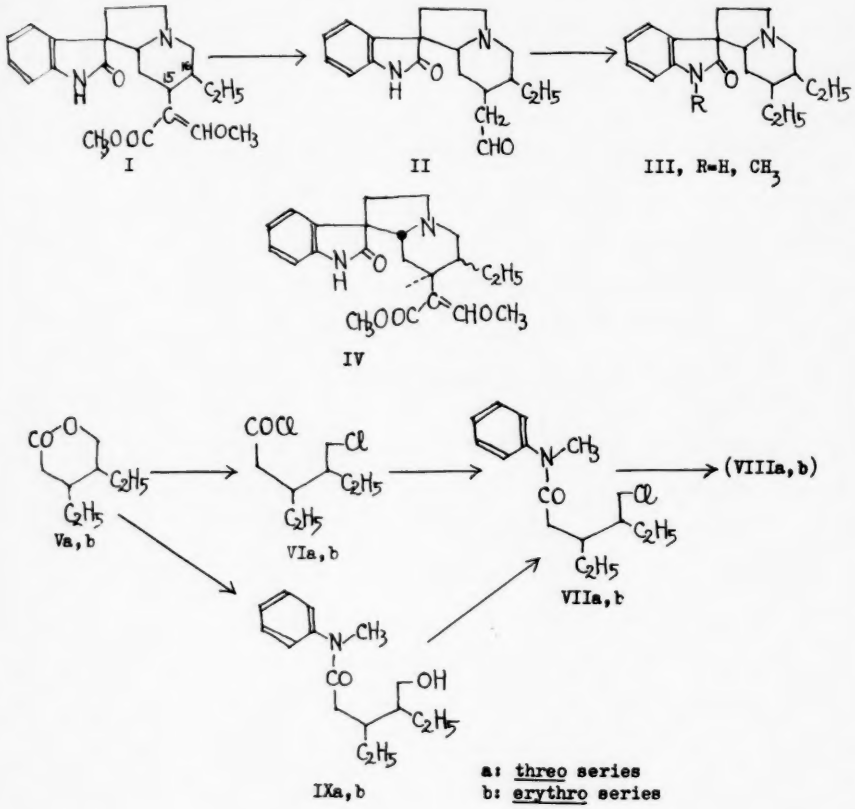
* Marion et al. prefer the name "isorhynchophyllane" to "rhynchophyllane" for this compound, because the same compound is obtained from isorhynchophylline and the isobase always predominates at the equilibrium of isomerization between rhynchophylline and isorhynchophylline.[2b] But we adopt the name "rhynchophyllane" till the stereochemistry of this base is elucidated.

1 H. Kondo, T. Fukuda and M. Tomita, J.Pharm.Soc.Japan 48, 321 (1928).

2a J.C. Seaton and L. Marion, Canad.J.Chem. 35, 1102 (1957); b J.C. Seaton and L. Marion, Ibid. 38, 1035 (1960).

3 T. Nozoye, Chem. & Pharm.Bull.Japan 6, 309 (1958).

4 H. Kondo and T. Ikeda, J.Pharm.Soc.Japan 57, 881 (1937).


I
II
III, R=H, CH3
IV
Va, b
VIa, b
VIIa, b
(VIIIa, b)
IXa, b
a: threo series
b: erythro series
X
VIIIa
XI
X
VIIIb
XII

In this paper, we wish to report stereospecific syntheses of four stereoisomers of rac.-N-methylrhynchophyllane, which established the trans configuration of the substituents at C(15) and C(16) of rhynchophylline and isorhynchophylline. The synthetic scheme is shown in the Chart.

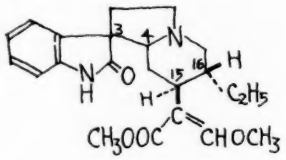
The lactone of threo-3:4-diethyl-5-hydroxyvaleic acid (Va)[5] was treated with phosphorus pentachloride to yield threo-3:4-diethyl-5-chlorovaleic acid chloride (VIa). This acid chloride, without purification, was condensed with methylaniline in pyridine to afford the anilide (VIIa, b.p. 158°/2.5 mm, Yield, 24.4% from Va) which in turn, was reduced with lithium aluminium hydride to give threo-3:4-diethyl-5-chlorovaleraldehyde (VIIIa, b.p. 110-112°/14 mm, Yield, 14.2%). The compound (Va) was reacted with methylanilinomagnesium iodide to yield IXa (b.p. 170-173°/3-4 mm, Yield, 60%) which, with thionyl chloride, gave VIIa, identical with the product obtained via the above route. The aldehyde (VIIIa) was condensed with N-methyloxytryptamine hydrochloride (X) in ethanolic solution of sodium hydroxide at room temperature for 7 days to afford pale yellow oil (yield, 56.7%), which was chromatographed on alumina. Elution with benzene yielded a main fraction of the free base (XI), colourless oil (called trans-A hereafter), giving the picrate, pale yellow prisms of m.p. 182-183°. Also, ether elution afforded the free base (XI), colourless oil (trans-B), yielding the picrate, orange yellow prisms of m.p. 184°.

On the other hand, the lactone of erythro-3:4-diethyl-5-hydroxyvaleic acid[5b] gave erythro-3:4-diethyl-5-chlorovaleic acid chloride (VIb), which was condensed with methylaniline to give the erythro-anilide (VIIb, b.p. 156-157°/2 mm, Yield, 57.5% from Vb). This anilide (VIIb) was reduced with

[5a] E.E. van Tamelen, P. Aldrich and T.J. Katz, J.Amer.Chem.Soc. 79, 6426 (1957); [b] A.R. Battersby and S. Garrett, J.Chem.Soc. 3512 (1959); Cf. C.F. Koelsch and C.H. Stratton, J.Amer.Chem.Soc. 66, 1881 (1944).

lithium aluminium hydride to yield erythro-3:4-diethyl-5-chlorovaleraldehyde (VIIIb, b.p. 105-108°/12 mm, Yield, 28%). The Grignard reaction of Vb gave the erythro-derivative (IXb, b.p. 173-174°/3-4 mm) in 60% yield, which was treated with thionyl chloride to afford the erythro-anilide (VIIb). Condensed with N-methyloxytryptamine hydrochloride (X) in ethanolic solution of sodium hydroxide, the aldehyde (VIIIb) gave the pale yellow oil (yield, 67.7%), which was purified by chromatography on alumina. Elution with benzene yielded a main fraction of the free base (XII), colourless needles, m.p. 94° (called cis-A hereafter), yielding the picrate, pale yellow scales of m.p. 173-174°. Similarly, benzene-ether (1:1) elution gave the colourless needles, m.p. 143-144° (XII, cis-B) which gave the picrate, orange yellow prisms, m.p. 168°. The infra-red spectra of these free bases (XI, trans-A and -B; XII, cis-A and -B) are very similar, but not identical particularly in 1150-1050 cm^{-1} region.

N-Methylrhynchophyllane (III, R=CH_3) derived from the natural alkaloid, was carefully chromatographed and obtained as colourless oil* which had the infra-red absorption in solution identical with that of the synthetic trans-A, but different from those of cis-A, cis-B and trans-B. The trans-arrangement at C(15) and C(16) of N-methylrhynchophyllane is thus established, which means that the relative configuration of the same positions of rhynchophyl-



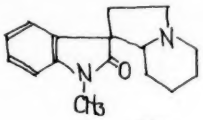
XIII

* This base gave the picrate, m.p. 185-186°, whose infra-red spectrum was completely identical with that of N-methylisorhynchophyllane, kindly supplied by Professor Marion.

line and isorhynchophylline are trans, because these alkaloids giving the same N-methylrhynchophyllane (III, R=CH_3) are considered to be different only in the configurations at C(3) and/or C(4),* and the above changes may be understood to take place without conversion of the configuration at C(15) and C(16).[5,6] Thus, rhynchophylline and isorhynchophylline are illustrated as the partial stereo-formula (XIII), in which the configurations at C(3) and C(4) of each alkaloid remain to be determined. Satisfactory elemental analyses have been obtained on every recrystallized product.

Acknowledgements - We are indebted to Professor Em.E. Ochiai and Dr. T. Nozoye for an authentic sample of rhynchophylline, and to Professor L. Marion for a I.R. chart of N-methylisorhynchophyllane.

* This interpretation was also supported by the fact that one of two isomers of the base (XIV) with no substituents at C(15) and C(16), recently synthesized by us, readily isomerizes to the other under the same conditions as the isomerization described above.[2b]



XIV

6 M.-M. Janot, R. Goutarel, A.Le Hir, G. Tsatsas and V. Prelog, Helv.Chim.Acta 38, 1073 (1955).

Tetrahedron Letters No.22, pp.796-801, 1961. Pergamon Press Ltd. Printed in Great Britain.

STUDIES ON THE STRUCTURE OF RUBREMETINIUM CATION: A NEW SYNTHESIS OF C-BISNORRUBREMETINIUM SALT AND ITS MODEL COMPOUND

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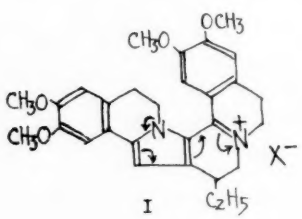
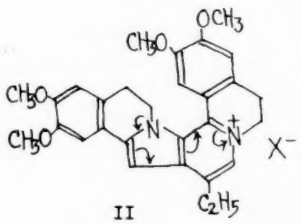
(Received 21 November 1961)

EMETINE is dehydrogenated with a variety of mild acidic oxidizing agents to afford so-called rubremetinium salt, which is the beautiful orange-red salt of a quaternary, monoacidic base. Although several structures had been suggested for the rubremetinium cation, the alternative structures, (I) and (II), have remained to be determined.[1]



I



II

The former formula ($C_{29}H_{33}O_4N_2X$) was proposed by Battersby et al.[2] and the latter ($C_{29}H_{31}O_4N_2X$) was preferred by Tietz and McEwen[3] who referred to it as Woodward's formulation. Thereafter, providing the further supporting data, Openshaw claimed the correctness of the formula (I).[1]

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[1] H.T. Openshaw, Chemical Society Special Publication No. 3, p.28. London (1955).

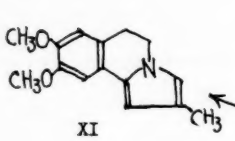
[2] A.R. Battersby, H.T. Openshaw and H.C.S. Wood, Experientia 5, 114 (1949).

[3] R.F. Tietz and W.E. McEwen, J.Amer.Chem.Soc. 75, 4945 (1953).

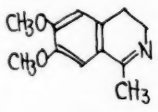
The total syntheses of this compound have already been achieved by several groups[4], but every known synthesis involved the oxidation process at the final step, which did not give the accurate number of hydrogen atoms eliminated from the penultimate product. This is the reason why none of these syntheses established its structure. In this paper, we wish to report a new synthesis of C-bisnorrubremetinium salt and its model compound of the same chromophore, without an oxidation process, which confirmatively supported the correctness of the formula (I) for rubremetinium cation.

A mixture of 1-methyl-3,4-dihydro-6,7-dimethoxyisoquinoline (III) and ethyl α-chloroacetoacetate (IVa) was refluxed in ethanol to afford the ester (Va), colourless needles, m.p. 91-20°, in 94% yield, which gave the hydrazide (Vb), colourless prisms, m.p. 197-198°. The ester was hydrolysed with 10% ethanolic solution of potassium hydroxide to the free acid (Vc), pale blue amorphous solid, m.p. 160-162° (decomp.), in 97% yield, which was readily decarboxylated by heating in benzene to XI, colourless prisms, m.p. 110-110.5°, in quantitative yield. A mixture of the free acid (Vc), 3,4-dimethoxyphenethyl amine and dicyclohexylcarbodiimide in chloroform was allowed to stand at room temperature to yield Vd, colourless needles, m.p. 171-173°, in 23% yield, which was cyclized with phosphorus pentoxide to a free base (VIb), pale yellow prisms, m.p. 165-167°, in 46% yield. This base was converted with dimethyl sulphate to the quaternary base (VIIb), red prismatic needles, m.p. 176-178°, quantitatively. The absorption spectra of VIb in N/100 HCl and VIIb of the same chromophore as that of formula (I),

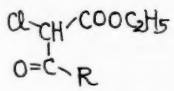
4 [a] A.R. Battersby and H.T. Openshaw, Experientia 6, 387 (1950); A.R. Battersby, H.T. Openshaw and H.C.S. Wood, J.Chem.Soc. 2463 (1953); [b] R.P.Evstigneeva, R.S. Livshits, L.I. Zakharkin, M.S. Bainova and N.A. Preobrazhenskii, Dok.Akad.Nauk SSSR 75, 539 (1950) [Chem.Abstr. 45, 7577 (1951)]; Zh.Obshchei Khim. (J.Gen.Chem.U.S.S.R.) 22, 1467 (1952) [Chem.Abstr. 47, 5949 (1953)]; [c] S. Sugasawa and Y. Ban, Proc.Japan Acad. 31, 31 (1955); Pharm.Bull.Japan 3, 53 (1955); T. Fujii, Chem. & Pharm.Bull.Japan 6, 591 (1958); [d] M. Pailer and G. Beier, Monatsh. 88, 830 (1957).



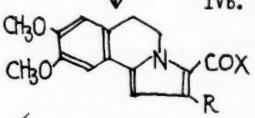
XI



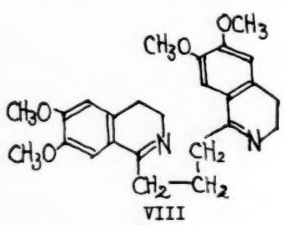
III



IVa. R=CH_3
IVb. R=$CH_2COOC_2H_5$

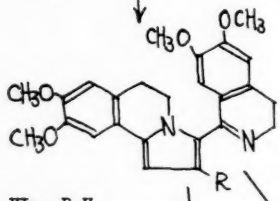


Va. R=CH_3, X=OC_2H_5
Vb. R=CH_3, X=$NHNH_2$
Vc. R=CH_3, X=OH
Vd. R=CH_3, X=3,4-$(CH_3O)_2C_6H_3CH_2CH_2N$
Ve. R=$CH_2COOC_2H_5$, X=OC_2H_5
Vf. R=CH_2COOH, X=OH
Vg. R=$CH_2COOC_2H_5$, X=OH
Vh. R=$CH_2COOC_2H_5$,
X=3,4-$(CH_3O)_2C_6H_3CH_2CH_2NH$-

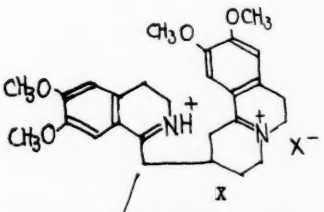


VIII

Battersby's work

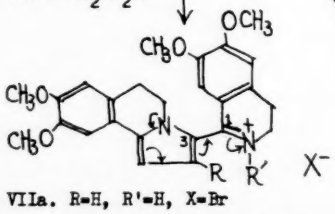


VIa. R=H
VIb. R=CH_3
VIc. R=$CH_2COOC_2H_5$
VId. R=CH_2CH_2OH

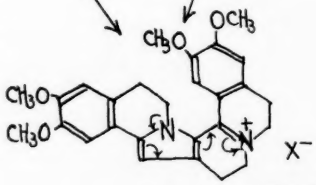


X

Sugasawa's work



VIIa. R=H, R'=H, X=Br
VIIb. R=CH_3, R'=CH_3, X=CH_3SO_4



IXa. X=p-$CH_3C_6H_4SO_3$
IXb. X=Br

are shown as curves (1) and (2) of Fig. 1, respectively, either of which is similar but not identical with that (curve (3)) of rubremetinium cation. This type of compound (VIa) was already synthesized by mercuric acetate oxidation of VIII by Battersby, quoted by Openshaw who stated that the

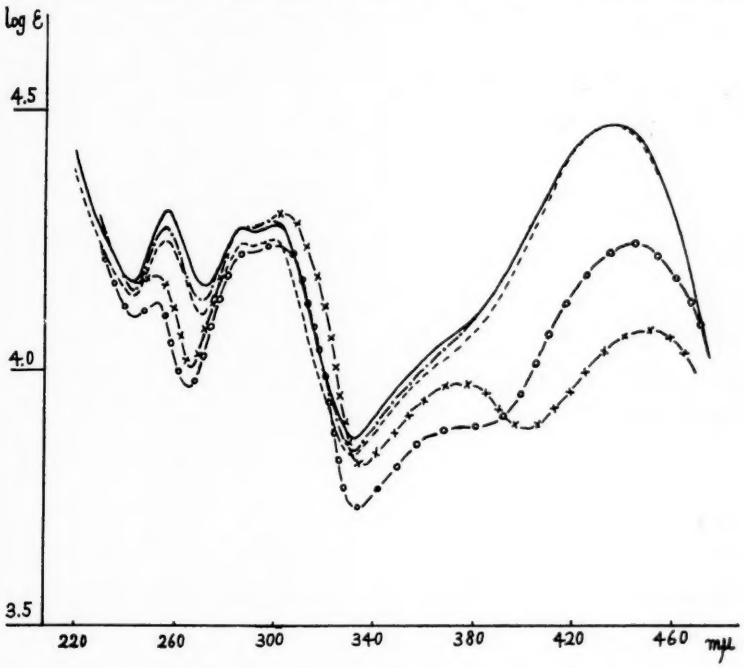


FIG. 1. Ultra-violet absorption spectra [in EtOH except (1)].
(1) —o—o— VIb in N/100 HCl
(2) —x—x— VIIb
(3) ———— (+)-Rubremetinium bromide (A.R. Battersby)[2]
(4) ---------- C-Bisnorrubremetinium bromide (M. Kirisawa)[5]
(5) — - — - C-Bisnorrubremetinium bromide (Present synthesis)

absorption spectrum of a solution of this salt (VIIa) was almost identical with that of rubremetinium bromide,[1] but the detail has not yet been published. Our experimental results described above are not enough for a decision between I and II, since the chromophoric system of these compounds (VIIb and VIb in HCl) can not be free from the effect induced by the inhibi-

tion of free rotation of the axis C(3)-C(1').

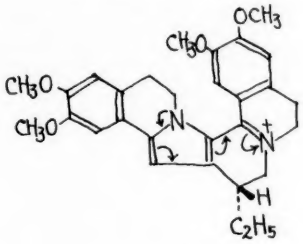
Thus, a new synthesis of bisnorrubremetinium salt was attempted with success, substituting IVb for IVa in the above synthesis. A mixture of III and IVb was refluxed in ethanol to afford the diester (Ve), colourless prisms, m.p. 95-97°, in 54% yield. The ester was hydrolysed to dicarboxylic acid (Vf), pale blue solid, m.p. 160-161° (decomp.), in 86.5% yield, which was decarboxylated by heating in xylene to XI, m.p. 110°, although in a poor yield. The dicarboxylic acid (Vf) was refluxed with acetic anhydride in benzene for 20 min to yield the corresponding anhydride, pale yellow needles, m.p. 216° (decomp.), in 92.5% yield which in turn, was refluxed in a mixture of pyridine and ethanol to give the half ester (Vg), pale pink needles, m.p. 148° (decomp.) in 79% yield. A mixture of Vg, 3,4-dimethoxyphenethyl amine and dicyclohexylcarbodiimide in chloroform was kept at room temperature to yield the amide (Vh), colourless needles, m.p. 132°, in 66% yield, which was boiled with phosphorus pentoxide in toluene for 5 hr to give VIc, pale yellow prisms, m.p. 136°, in 47.2% yield. This ester was reduced with lithium aluminium hydride in a boiling mixture of ether and tetrahydrofuran for 3 hr to yield the alcohol (VId), pale yellow needles of a reasonable ultra-violet absorption spectrum identical with those of VIb and VIc, m.p. 163-164°, in 66% yield. Thus, a mixture of the alcohol (VId) and tosyl chloride in benzene was allowed to stand at room temperature, producing IXa, orange needles, m.p. 192-194°, quantitatively, which was readily converted to the corresponding bromide (IXb), orange red needles, m.p. 215° (lit. m.p. 236-237° as trihydrate,[5] and m.p. 215°[6]). The infrared spectrum of this bromide was identical with that of C-bisnorrubremetinium bromide kindly supplied by Professor Sugasawa and Dr. Kirisawa who obtained

[5] M. Kirisawa, Chem. & Pharm.Bull.Japan 7, 38 (1959).

[6] M. Pailer and H. Strohmayer, Monatsh. 83, 1198 (1952).

their product by mercuric acetate oxidation of X.[5] The absorption spectra (curves (4) and (5) of Fig. 1) of the bromide (IXb) are in good agreement with that of rubremetinium cation, showing that both compounds have the same chromophore.

Since it could be generally accepted that dehydrogenation does not occur at the final step of the present synthesis of IXa and IXb, the formula (I) and accordingly the formula (XII) in terms of the absolute configuration[7] for rubremetinium cation are confirmatively supported. Good elemental analyses have been obtained on every recrystallized product.



XII

Acknowledgements - We are indebted to Professor Em.S. Sugasawa and Dr. M. Kirisawa for generous gifts of a sample and the infra-red spectrum of C-bisnorrubremetinium bromide.

[7] E.E. van Tamelen and J.B. Hester, J.Amer.Chem.Soc. 81, 507 (1959); A.R. Battersby and S. Garratt, Proc.Chem.Soc. 86 (1959); Y. Ban, M. Terashima and O. Yonemitsu, Chem. & Ind. 569 (1959).

Tetrahedron Letters No. 22, pp.802-806, 1961. Pergamon Press Ltd. Printed in Great Britain.

1961

OPTICALLY ACTIVE CUMULENE

SYNTHESIS AND RESOLUTION OF 1,5-DI-p-CHLOROPHENYL-1,5-DI-t-BUTYL-PENTATETRAENE

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(Received 23 October 1961)

AS early as 1875, van t'Hoff had predicted that an unsymmetrically substituted cumulene should be resolvable into optical antipodes, when the number of its cumulative double bonds is even,[1] but this prediction has not been verified up to now except for allenes.[2] With regard to pentatetraenes, having four cumulative double bonds, even the synthesis of a symmetrically substituted product has not yet been attained.[3] The isolation of cis- and trans-isomers of butatrienes which contain an odd number of cumulative double bonds has been reported recently by Kuhn[4]. But their geometrical stability is so small that they can be interconverted very easily.

It is now of interest to clarify whether pentatetraenes can be resolved

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[1] J.H. van t'Hoff, La Chimie dans L'Espace. Rotterdam (1875).

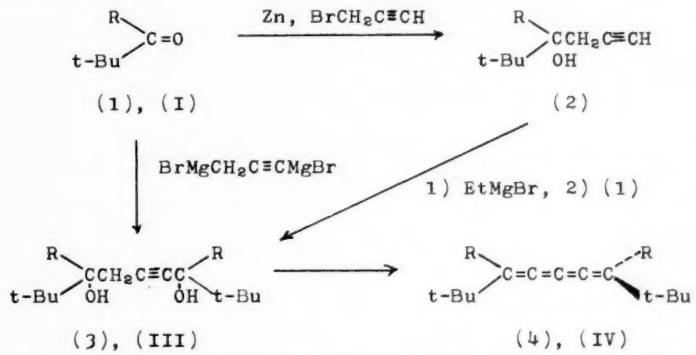
[2] P. Maitland and W.H. Mills, Nature, Lond. 135, 994 (1935); J.Chem. Soc. 879 (1936); E.P. Kohler and M. Tischler, J.Amer.Chem.Soc. 57 1743 (1935).

[3] The first report on the synthesis of bis-pentatetraene [Angew.Chem. 70, 705 (1958)] has been corrected, see R. Kuhn and H. Fischer, Chem.Ber. 92, 1849 (1959).

[4] R. Kuhn and K.L. Scholler, Chem.Ber. 87, 598 (1954); R. Kuhn and D. Blum, Ibid. 92, 1483 (1959).

into enanthiomorphs as in the case of allenes, or whether the resolution of them is possible in view of the extreme ease of interconversion of butatrienes.

We have now achieved the synthesis of pentatetraenes according to the following route*.



(1), (I) (2) (3), (III) (4), (IV)

Starting from phenyl t-butyl ketone (1), we have obtained the acetylenic glycol (3) via the acetylenic alcohol (2) or directly by means of Kuhn's method[3]. Dehydration of (3) by the action of p-toluenesulphonic acid in boiling benzene and subsequent purification on chromatography yielded (4) as colourless prisms (from methanol), m.p. 99~100°C, $C_{25}H_{28}$ (Found: C, 90.77; H, 8.50%).

The ultra-violet spectrum of this hydrocarbon shows the following absorption maxima in ethanol. λ_{max} : 229; 261; 304; 312 and 340 (inflexion) mμ (ε = 14,700; 36,600; 10,200; 9500 and 3400). The infra-red spectrum of (4) shows a strong band at 1940 cm^{-1} which is characteristic of the cumulene structure. The formula of (4) was assigned to this hydrocarbon on the basis of the above-mentioned spectroscopic data and the following evidence.

This hydrocarbon absorbed 3 moles of hydrogen in ethyl acetate and

* Arabic numerals: R=phenyl ; Roman numerals: R=p-chlorophenyl.

acetic acid over palladium oxide. When platinum oxide was used as catalyst, the absorption did not stop at 4 moles, but slow absorption continued without appreciable change in the absorption rate. This anomalous behaviour in catalytic reduction is not inconsistent with the assigned formula, since the reference compound, 1,4-diphenyl-1,4-di-t-butyl-butatriene, synthesized according to the method of Bohlmann[5] also absorbed only 2 moles of hydrogen over palladium oxide, and the absorption did not stop at 3 moles over platinum oxide.

The NMR spectrum of (4) in carbon tetrachloride (0.5 mole solution) shows two lines arising from methyl protons in the aliphatic region (+141 cps and +146 cps at 40 MC using water as external standard). The doublet methyl resonance would be due to the bulky t-butyl group, which tends to fix the methyl groups to a certain extent. The fact that the NMR spectrum of the similarly substituted butatriene also shows two lines with the same chemical shift as (4) indicates that the t-butyl groups in both compounds are in very similar environments.

In order to obtain the pentatetraene (4) in optically active form we applied the method of asymmetric dehydration of the glycol (3) by the action of d-bromocamphorsulphonic acid. The fractional recrystallization of the dehydration product afforded (4), colourless prisms, m.p. 95-96°C, showing the specific rotation $[\alpha]_{5461} = +11^{\circ}$ in benzene solution. Owing to the low optical yield and the minor differences[3] of solubility between the active form and the racemate, we were unable to obtain the optically pure enantiomorph.

To overcome the above-mentioned difficulties, the synthesis of the p-chloro-substituted analogue of (4) was carried out according to the same sequence of reactions. Treatment of the glycol (III) with d-bromocamphor-

[5] F. Bohlmann and K. Kieslich, Chem.Ber. 88, 1211 (1955).

sulphonic acid in benzene afforded the dehydration product. Chromatographic purification of the product furnished pale yellow crystals, $C_{25}H_{26}Cl_2$, m.p. 171~172°C, (Found: C, 75.87; H, 6.64%). The ultra-violet spectrum of this substance (in ethanol, λ_{max} : 207.5; 234; 267; 300 and 311 mμ (ε = 33,000; 17,300; 39,200; 9900 and 8100) closely resembles that of (4). Also the infra-red spectrum exhibits a strong absorption at 1940 cm^{-1} indicating the presence of the cumulene structure. From these observations the structure of 1,5-di-p-chlorophenyl-1,5-di-t-butylpentatetraene (IV) was given to the pale yellow hydrocarbon.

Fortunately, spontaneous partial resolution was observed in the fractional recrystallization of IV (m.p. 171~172°C, $[\alpha]_{5461}$ = +0.3° (c = 4.40)* from a mixture of ethanol and methanol (1 : 3.3). The laevorotatory crystals (first crop, $[\alpha]_{5461}$ = -27.2°, second crop, $[\alpha]_{5461}$ = -29.3°) were obtained on cooling the solution. These two crops were combined and fractionally recrystallized from the same solvent. Increasing values of rotation in the more soluble fractions was observed, and finally pale yellow crystals, m.p. 157~158.5°C, $[\alpha]_{5461}$ = -467° (c = 0.120) were obtained from the most soluble fraction. The dextrorotatory mother liquor of the above-mentioned laevorotatory first and second crops was fractionally concentrated in the same way. Pale yellow crystals (m.p. 158~159°C, $[\alpha]_{5461}$ = +447° [c = 0.518]) were obtained from the most soluble fraction. Further recrystallization of the laevo-IV caused a minor change in the optical rotation and therefore, the optical purity of these antipodes seems to be fairly high. The ultra-violet and infra-red spectra of d-, l- and rac-IV were found to be completely identical over the entire region of the spectrum. The rate of racemization of the laevo-isomer was measured in bromobenzene at 156°C and the half-life period was found to be ca. 700 min.

* The optical rotation was measured in benzene solution throughout this experiment.

The optical stability of (IV) is similar to that of the optically active allenes[2] in sharp contrast to the geometrical instability of butatrienes.[4] The marked difference of the stability between the two series of compounds (even number and odd number of the cumulative double bonds) seems to be reflected in the ultra-violet spectra. As we have synthesized a number of variously substituted pentatetraenes, the discussion about this point will be presented separately.

The van't Hoff's prediction of the existence of the optically active higher homologues of allene is now verified experimentally by the above-mentioned resolution of 1,5-di-p-chlorophenyl-1,5-di-t-butyl-pentatetraene (IV).

The details of this research will be reported elsewhere.

Tetrahedron Letters No. 22, pp.807-810, 1961. Pergamon Press Ltd. Printed in Great Britain.

DIE REAKTION VON TRIPHENYLPHOSPHIN-METHYLENEN MIT DIAZONIUMSALZEN. DARSTELLUNG VON TRIPHENYLPHOSPHIN-ARYLAZO-METHYLENEN

Gottfried Märkl

Chemisches Institut der Universität Würzburg

(Received 21 November 1961)

Triphenylphosphin-methylene (I) addieren Diazoniumsalze zu den Phosphoniumsalzen II, die sich unter der Einwirkung von Basen in die Triphenylphosphin-arylazo-methylene III überführen lassen:

$$[(C_6H_5)_3P{=}CHR \underset{I}{\leftrightarrow} (C_6H_5)_3\overset{\oplus}{P}\text{-}\overset{\ominus}{C}HR\ ] + R'\text{-}\overline{N}{=}\overset{\oplus}{N}\text{-}R'\ ]\ X^{\ominus} \rightarrow$$

$$[(C_6H_5)_3\overset{\oplus}{P}\text{-}\underset{\underset{\underline{N}=\underline{N}\text{-}R'}{|}}{CHR}\ ]\ X^{\ominus} \rightarrow \underset{III}{(C_6H_5)_3P{=}\underset{\underset{R}{|}}{C}\text{-}\overline{N}{=}\overline{N}\text{-}R'}$$

II

Die in wässrigen Systemen infolge Resonanzstabilisierung beständigen Phosphor-Ylide I (R = $-COOCH_3$, $-COCH_3$, $-COC_6H_5$, $-CONH_2$, $-CN$) lassen sich nach drei verschiedenen Methoden zu den Azo-Yliden III umsetzen:

A. In die wässrig methanolische Lösung von I werden äquimolare Mengen eines Diazoniumfluoborats eingetragen. Nach der praktisch augenblicklich verlaufenden Umsetzung, die sich an der Farbbildung zu erkennen gibt, läßt sich das Phosphoniumsalz II ($X = BF_4^{\ominus}$) mit Wasser ausfällen. Mit wässriger Natronlauge erhält man direkt die Azo-Ylide III.

B. Die Lösung der zu I gehörigen Phosphoniumsalze

$[(C_6H_5)_3P\text{-}CH_2R]$ X (X = Cl,Br) in Wasser oder Methanol/Wasser wird bei 0° mit einer frisch bereiteten Diazoniumsalzlösung versetzt.Unter intensivem Rühren tropft man 2n Natronlauge bis zur Ausfällung des Azo-Ylids III zu.

C. In der Lösung von I in wenig Methanol löst man eine äquimolare Menge N-Nitrosoacetanilid.Nach etwa 30 Minuten beginnt direkt das Azo-Ylid III in sehr reiner Form auszukristallisieren.

Das Verfahren B kann zur Darstellung der Azo-Ylide III aus weniger beständigen Phosphor-Yliden I nur dann herangezogen werden,wenn die Kuppelungsreaktion von I wesentlich schneller verläuft als deren Hydrolyse.Die leicht hydrolysierenden Phosphor-Ylide I (R = $-CH{=}CH\text{-}COOCH_3$,$-(CH{=}CH)_2\text{-}COOCH_3$, $-p\text{-}C_6H_4NO_2$, $-o\text{-}C_6H_4NO_2$) lassen sich nach dieser Methode noch in die Azo-Ylide III überführen.

Für die stärker basischen,nicht resonanzstabilisierten Triphenylphosphin-methylene I (R = $-C_6H_5$,-Alkyl , -H) sind die Methoden A – C zur Darstellung von III nicht geeignet,da sich unter der Einwirkung wässriger Alkalien diese Ylide nicht mehr bilden.Nach der Alkoholat-Methode in absolutem Methanol oder Äthanol bereitete Ylid-Lösungen zersetzen sich mit festen Diazoniumfluoboraten $R\text{-}N_2$] BF_4 (R = $-C_6H_5$, - $p\text{-}C_6H_4NO_2$) unter Stickstoffabspaltung.

Zur Bildung der hydrolyseempfindlichen Ylide I aus ihren Phosphoniumsalzen wurde nun die noch nicht beschriebene Umsetzung mit Kalium-tert.Butylat herangezogen.Nach 60-90 minütigem Schütteln in absolutem Benzol oder Toluol haben sich die Salze praktisch völlig unter Bildung der roten Ylidlösungen umgesetzt.

Sowohl die Reaktion dieser Ylid-Lösungen mit in Benzol oder Toluol suspendierten Diazoniumfluoboraten als auch die Umsetzung mit N-Nitrosoacetanilid in Benzol-Lösung verlaufen ebenfalls nicht glatt zu den Azo-Yliden III.Bei der näher untersuchten Umsetzung von Triphenylphosphin-benzylen (R = $-C_6H_5$) bildet sich neben einer geringen Menge Azo-Ylid III überwiegend Triphenyl-formazan.Es zeichnet sich somit ein Reaktionsverlauf ab,bei dem intermediär gebildetes freies Azo-Ylid III mit einem weiteren Mol Diazoniumverbindung zu einem Phosphoniumsalz IV weiterreagiert,das durch Hydrolyse in Triphenylphosphinoxyd und Triphenyl-formazan zerlegt wird:

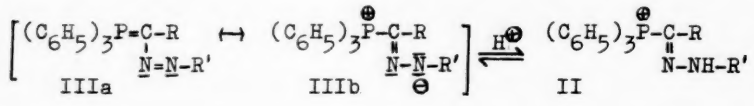
$$\underset{\text{II}}{[(C_6H_5)_3\overset{\oplus}{P}-\underset{N=N-C_6H_5}{\underset{|}{C}}HC_6H_5}\ ]\ X^{\ominus} + (C_6H_5)_3P{=}CHC_6H_5 \rightleftharpoons \underset{\text{III}}{(C_6H_5)_3P{=}\underset{N=N-C_6H_5}{\underset{|}{C}}-C_6H_5} + [(C_6H_5)_3\overset{\oplus}{P}-CH_2C_6H_5]\ X^{\ominus}$$

$(X^{\ominus} = BF_4^-, OCOCH_3^-)$

$$\text{III} + C_6H_5\overset{\oplus}{N_2}]\ X^{\ominus} \rightarrow \left[\underset{\text{IV}}{(C_6H_5)_3\overset{\oplus}{P}-\underset{N=N-C_6H_5}{\overset{N=N-C_6H_5}{\underset{|}{\overset{|}{C}}}}-C_6H_5}\right] X^{\ominus} \rightarrow (C_6H_5)_3PO +$$

$$C_6H_5-N=N-\underset{C_6H_5}{\underset{|}{C}}=N-NH-C_6H_5 + HX$$

Die bisher dargestellten und untersuchten Azo-Ylide III sind gelbe bis blauviolette Verbindungen,die relativ hydrolysebeständig sind und erst nach längerem Kochen in wässrigem Methanol zerlegt werden.Die Azo-Gruppe bewirkt also eine zusätzliche Resonanzstabilisierung (IIIa ↔ IIIb).Die ausgeprägte kurzwellige Verschiebung der Spektren im sichtbaren und nahen UV-Bereich in methanolischer Lösung gegenüber Benzol als Lösungsmittel sowie das Auftreten isosbestischer Punkte sprechen für die Ausbildung von Protonierungsgleichgewichten III ⇌ II:



IIIa IIIb II

Daß die Phosphoniumsalze in der Hydrazonform II vorliegen, ergibt sich aus IR-spektroskopischen Untersuchungen.

In der Tabelle werden einige der nach den verschiedenen Methoden dargestellten Azo-Ylide beschrieben.

Azo-Ylid III $(C_6H_5)_3P{=}C(R)-N{=}N-R'$	Schmp. °C	Methode	Ausbeute in %	Farbe	λ + in mμ
R= $-COOCH_3$ R'= $-C_6H_5$	197-198	A,B,C	96;98;91	gelb	360
R= $-COOCH_3$ R'= $-p-C_6H_4NO_2$	196-198	B	100	ziegelrot	450
R= $-(CH{=}CH)_2-COOCH_3$ R'= $-p-C_6H_4NO_2$	amorph	B	78	blau-violett	566; 590
R= $-COC_6H_5$ R'= $-C_6H_5$	160-162	A,C	100;94	orange	370
R= $-p-C_6H_4NO_2$ R'= $-C_6H_5$	146-147	B	89	tiefrot grüner Metallglanz	512

+Lage der langwelligsten Maxima in Benzol-Lösung

Das Studium der Azo-Ylide wird in verschiedenen Richtungen, insbesondere im Hinblick auf ihre Fähigkeit zu Olefinierungsreaktionen unter Bildung von Äthylenazofarbstoffen fortgesetzt.

Herrn Prof.Dr.A.Roedig bin ich für die Unterstützung dieser Arbeiten zu großem Dank verpflichtet, den Farbenfabriken Baeyer, Werk Leverkusen, danke ich für die Überlassung von Chemikalien.

Tetrahedron Letters No. 22, pp.811-813, 1961. Pergamon Press Ltd. Printed in Great Britain.

DIE REAKTION VON TRIPHENYLPHOSPHIN-METHYLENEN MIT ALIPHATISCHEN DIAZOVERBINDUNGEN

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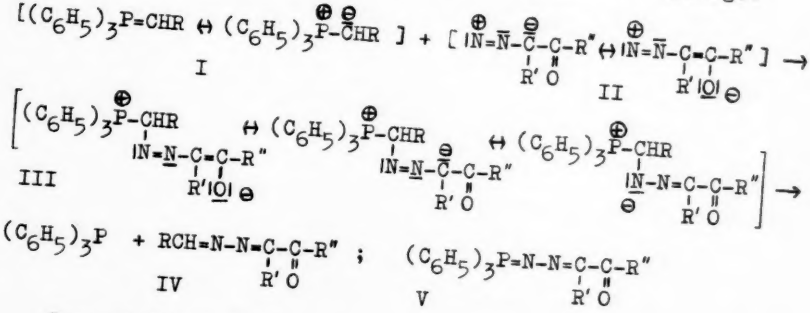
STARK nucleophile Triphenylphosphin-methylene I reagieren mit aliphatischen Diazoverbindungen II, wenn deren elektrophile Reaktionsbereitschaft durch Substituenten mit negativem mesomeren Effekt erhöht ist. Dem primären Reaktionsschritt einer Addition von II an I folgt eine Stabilisierung des intermediären Adduktes III, die überraschend nicht durch die Verschiebung des Protons vom ursprünglichen Ylid-Kohlenstoffatom an das freie Elektronenpaar einer der mesomeren Grenzstrukturen von III, sondern unter Fragmentierung zu Triphenylphosphin und das entsprechende gemischte Azin IV erfolgt:



Das gebildete Triphenylphosphin setzt sich mit einem weiteren Mol aliphatischer Diazoverbindung II zu dem Phospha-

zin V um.

Die Umsetzungen werden bei Raumtemperatur in absolutem Benzol oder Toluol durchgeführt.Das aus Azin IV und Phosphazin V bestehende Reaktionsgemisch läßt sich durch fraktionierte Kristallisation aus absolutem Äther oder Methanol oder durch Chromatographie an Aluminiumoxyd auftrennen.Die Tabelle bringt eine Übersicht der Reaktionsprodukte von Triphenylphosphinbenzylen (I,R = $-C_6H_5$) mit verschiedenen Diazoverbindungen II.

Diazoverbindung $R''-\overset{O}{\overset{\|}{C}}-\overset{N_2}{\overset{\|}{C}}-R'$ II	Phosphazin $(C_6H_5)_3P=N-N=\overset{R'}{\overset{\|}{C}}-\overset{O}{\overset{\|}{C}}-R''$			Azin $C_6H_5CH=N-N=\overset{R'}{\overset{\|}{C}}-\overset{O}{\overset{\|}{C}}-R''$		
	Schmp.°C Gef.	Lit.	Ausb. %	Schmp.°C Gef.	Lit.	Ausb. %
$R'=-COOCH_3$ $R''=-C_6H_5$	136-138	138-140 [1]	100	108-110	-	34
$R'=-COOC_2H_5$ $R''=-CH_3$	$(C_6H_5)_3P$ +		69	91-93	-	50
$R'=-C_6H_5$ $R''=-C_6H_5$	116-117	116-118	62,5	150-151	151 [2]	90
$R'=-H$ $R''=-C_6H_5$	119-120	119-120 [3]	80	++	-	

\+ Diazoacetessigester setzt sich unter den Reaktionsbedingungen noch nicht mit Triphenylphosphin um

++ In dem nicht kristallisierenden Öl durch saure Spaltung in Benzaldehyd,Phenylglyoxal und Hydrazin nachgewiesen

[1] H.Staudinger u.G.Lüscher,Helv.chim.Acta 5,75 (1922).

[2] T.W.J.Taylor,N.H.Callow u.C.R.W.Francis,J.chem.Soc. [London] 257 (1939).

[3] H.J.Bestmann u.H.Fritzsche,Ber.dtsch.chem.Ges.94,2478 (1961).

Die Umsetzung von Triphenylphosphin mit II zu den Phosphazinen V verläuft - mit Ausnahme des Diazoacetessigesters - schneller als die Addition von II an Triphenylphosphin-benzylen, da auch bei äquimolaren Mengen der Reaktionspartner ein Gemisch von Phosphazin und Azin gebildet wird.

Andere untersuchte Triphenylphosphin-methylene (R = -H , $-CH_3$, $-C_2H_5$, $-C_3H_7$) zeigen einen entsprechenden Reaktionsverlauf, wenngleich sich bei einigen Diazoverbindungen II Nebenreaktionen abzeichnen, über die später berichtet wird.

Die weniger reaktionsfähigen Phosphor-Ylide I (R = $-COCH_3$, $-COC_6H_5$, $-COOCH_3$) reagieren unter den angegebenen Reaktionsbedingungen nicht.

Die Untersuchungen werden in verschiedenen Richtungen fortgesetzt.

Ich danke Herrn Prof.Dr.A.Roedig für die Förderung dieser Arbeit, den Farbenfabriken Baeyer, Werk Leverkusen, für die großzügige Überlassung von Chemikalien.

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1961

THE ABSOLUTE CONFIGURATION OF ECHITAMINE IODIDE

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(Received 27 November 1961)

ECHITAMINE iodide ($C_{22}H_{29}O_4N_2I$) crystallizes in the orthorhombic system (space group : $P2_12_12_1$; axial dimensions : $\underline{a}$ = 18.45 Å, $\underline{b}$ = 13.83 Å, c = 8.48 Å) with four molecules in the unit cell. From intensity data of the hko, hol and okl zones obtained by the Weissenberg technique, its crystal structure has been solved by X-ray methods. The molecular structure confirms the configuration deduced from the hko projection[1] and also agrees well with that obtained earlier by Robertson et al.[2] for echitamine bromide ($C_{22}H_{29}O_4N_2Br$, MeOH) using three-dimensional data.

The absolute configuration of the molecule has also been fixed by the application of Bijvoet's[3] technique making use of the anomalous scattering of CuK_α radiation by the iodine atoms.[4] The atomic arrangement of the quarternary echitamine ion as viewed down the $\underline{c}$ axis is shown in the correct absolute orientation in Fig. 1, while the more conventional representation is given in Fig. 2 (a). The disposition of the various groups in the latter figure are indicated with respect to the substituted cyclohexane ring which

[1] H. Manohar and S. Ramaseshan, Curr.Sci. 30, 5 (1961).

[2] J. A. Hamilton, T.A. Hamor, J. Monteath Robertson and G.A. Sim, Proc.Chem.Soc. 63 (1961).

[3] J.M. Bijvoet, A.F. Peerdeman and A.J. van Bommel, Nature, Lond. 16, 271 (1951).

[4] C.F. Dauben and D.H. Templeton, Acta Cryst. 8, 841 (1955).

1961

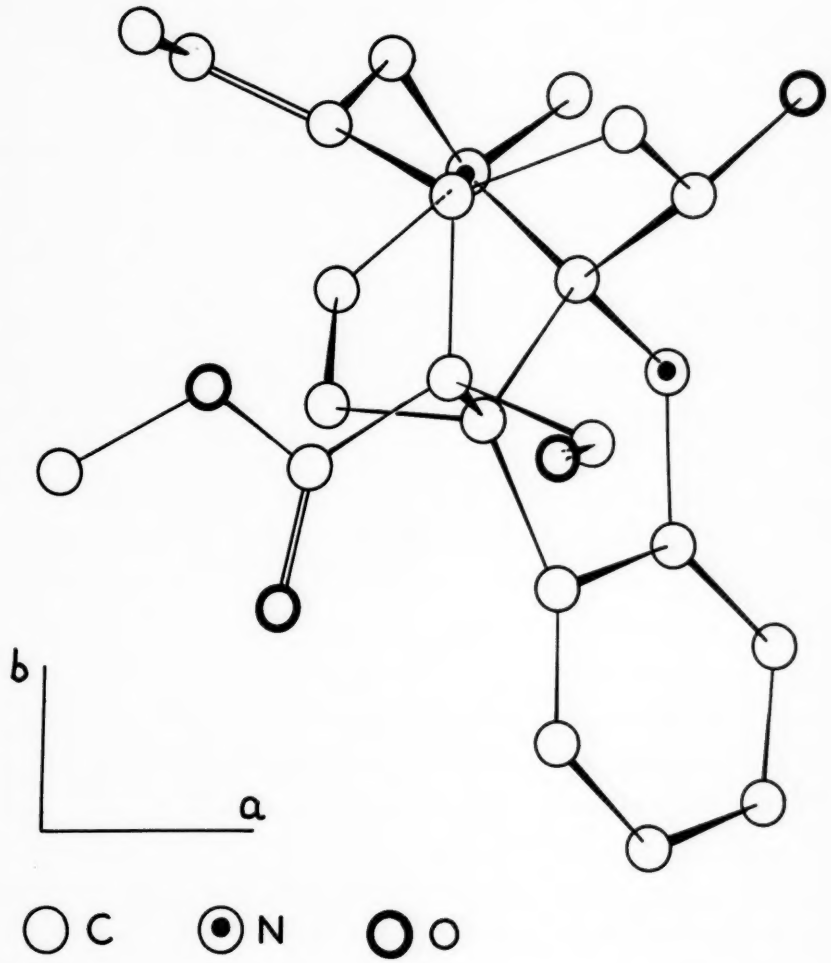

FIG. 1.

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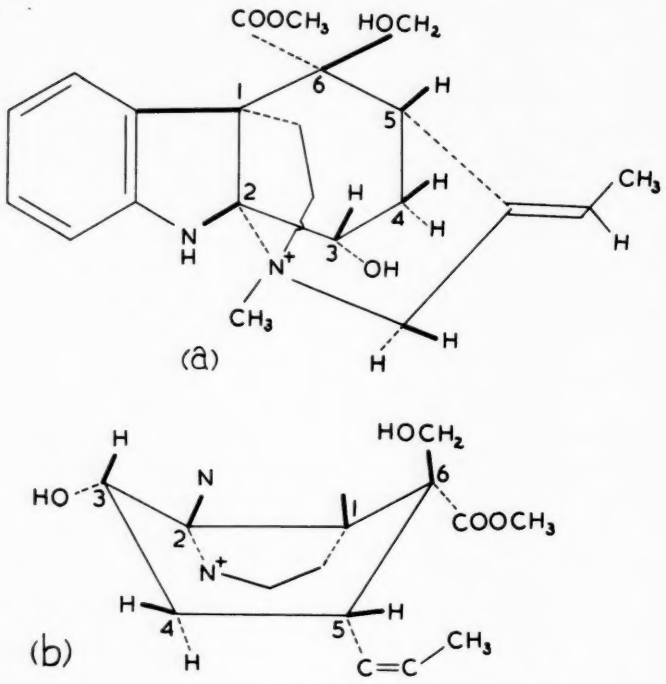

FIG. 2

is actually in the form of a boat with carbon atoms (3) and (6) above the plane of the paper. This representation of the cyclohexane ring with the different attached groups is shown separately in Fig. 2 (b).

The CH_2OH and H are in the flag-pole positions while the $COOCH_3$ and OH groups, and the H atom linked to C (5) are equatorial in relation to the six-membered ring. The five-membered ring containing the quarternary nitrogen is below while the five-membered ring of the dihydro-indole nucleus is above. The methyl group of $= C - CH_3$ is cis to C (5).

The details of the X-ray analysis are under publication.

The authors wish to thank Professor T.R. Govindachari for samples of the crystal, and Professor R.S. Krishnan for his kind interest in the problem.

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BASE CATALYSED REARRANGEMENTS OF α-KETOLS

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The Weizmann Institute of Science,

Rehovoth, Israel

(Received 27 November 1961)

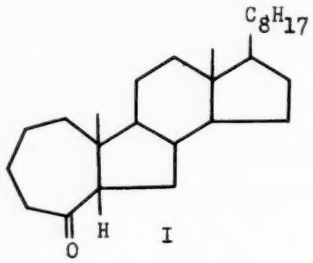
RECENTLY we have described a conversion of decalins into perhydroazulenes using an irreversible pinacolic type rearrangement.[1] We wish to report now a conversion of perhydroazulenes to decalins using a reversible, base catalysed stereospecific α-ketol rearrangement.

A-homo-B-nor-6βH-cholestan-5-one (I)[1] was reduced with lithium aluminium hydride to the corresponding alcohol (II, R=H, m.p. 57-59°; $[\alpha]_D$ +46°) which was tosylated in pyridine to give (II, R=Ts, m.p. 97-98°; $[\alpha]_D$ + 21°). The tosylate with lithium aluminium hydride in tetrahydrofuran or with sodium iodide in 2-butanone underwent elimination to the olefin (III, m.p. 84-86°; $[\alpha]_D$ -2°). Treatment of III with osmium tetroxide in pyridine yielded the diol (IV, m.p. 142-144°; $[\alpha]_D$ +44°), which was then oxidized with pyridine-chromate to the ketol (V, m.p. 188-189°; $[\alpha]_D$ +31°).

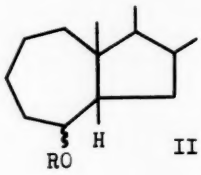
The stereochemistry of V was established from its infra-red and ultra-violet absorption spectra. The hydroxyl stretching frequency indicated intramolecular hydrogen bonding[2] (Table 1). The maximum in the ultra-violet associated with the carbonyl group was shifted hypsochromically by

[1] Y. Mazur and M. Nussim, J.Amer.Chem.Soc. 83, 3911 (1961).

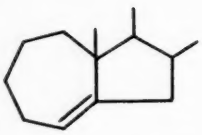
[2] For analogous systems see: A.C. Huitric and W.D. Kumler, J.Amer. Chem.Soc. 78, 1147 (1956).



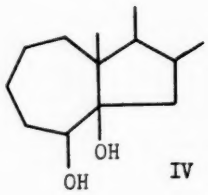
I



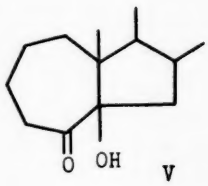
II



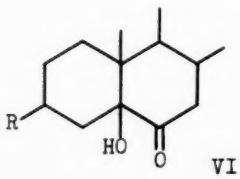
III



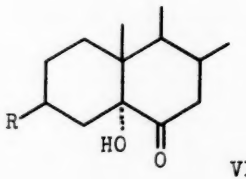
IV



V



VI



VII

5 mμ because of the adjacent hydroxyl group;[3] this is supported by the position of the first maximum in the rotatory dispersion curve[4] (Table 2). Both values indicated the proximity of the $\rangle$C-OH and —C=O groups. This is possible only when the seven- and the five-membered rings of V are cis fused; hence the angular hydroxyl is in the β-position.

Ketol V on boiling for 1 hr in methanolic potassium hydroxide (2%) rearranged to the isomeric ketol (VI, R=H).[5]

A perhydroazulene ketol was postulated by Shoppee et al. to explain the formation of cholestane-5β,6α-diol on reducing cholestane-5α-ol-6-one (VII,

[3] R.C. Cookson and S.H. Dandegaonker, J.Chem.Soc. 352 (1955).

[4] Cf. C. Djerassi, Optical Rotatory Dispersion pp.111-114. McGraw-Hill, New York (1960).

[5] D.N. Jones, J.R. Lewis, C.W. Shoppee and G.H.R. Summers, J.Chem.Soc. 2876 (1955).

Table 1
OH Stretching Frequencies in cm^{-1}*

	Free OH	Hydrogen bonded OH
V		3495
VI R=H		3505
VI R=OH	3612	3515
VII R=H	3615	
VII R=OH	3612	

* All measurements were made with a Perkin-Elmer infra-red spectrometer, Model 12 C, in carbon tetrachloride (c 0.0012 moles/l.).

R=H) with sodium in n-propanol.[5] This prompted us to investigate the possible base isomerization of this ketol. Treatment of the trans-ketol (VII, R=H) with boiling methanolic potassium hydroxide (10%) for 8 hr resulted in 92% conversion to the cis-ketol (VI, R=H). The same equilibrium mixture was obtained on treating (VI, R=H) similarly. This thermodynamic equilibrium corresponds to a free energy difference of 1.7 kcal $mole^{-1}$. The main contribution to the stability of (VI, R=H) comes probably from the hydrogen bonding between the hydroxyl and carbonyl as indicated by the hydroxyl stretching frequency at 3500 cm^{-1} in the infra-red as compared with the non-bonded hydroxyl frequency at 3612 cm^{-1} of (VII, R=H) (Table 1).[6]

Similar rearrangements of α-ketol systems were studied extensively in the D-homo-steroids, where stereospecificity and reversibility were established. The assumption was made that the concerted electron shift leads to a product in which the C-OH bond assumes the same direction in space as the respective C=O bond in the parent compound.[7]

[6] For relations between OH frequency differences and energy differences due to hydrogen bonding; R.M. Badger and S.H. Bauer, J.Chem.Phys. 5, 839 (1937).

[7] Cf. inter al., R.B. Turner, J.Amer.Chem.Soc. 75, 3484 (1953); N.L. Wendler, D. Taub and R.W. Walker, Tetrahedron 11, 163 (1960).

Table 2
Ultra-violet and Rotatory Dispersion Data

Substance	U.V. max mμ	RD first extremum mμ	[A]
I	289	312.5	+ 85
V	284	302.5	- 26
Coprostan-6-one	292	312.5**	- 113**
VI R=H	284	302.5	- 144
VI R=OAc	281	302.5	- 186
3β-Acetoxy-cholestan-6-one	291	306**	- 76**
VII R=H	302	320	- 83
VII R=OAc	303	322.5	- 110

* All measurements were taken in dioxane; [A], the amplitudes as defined by C. Djerassi and W. Klyne, Proc.Chem.Soc. 55 (1957).

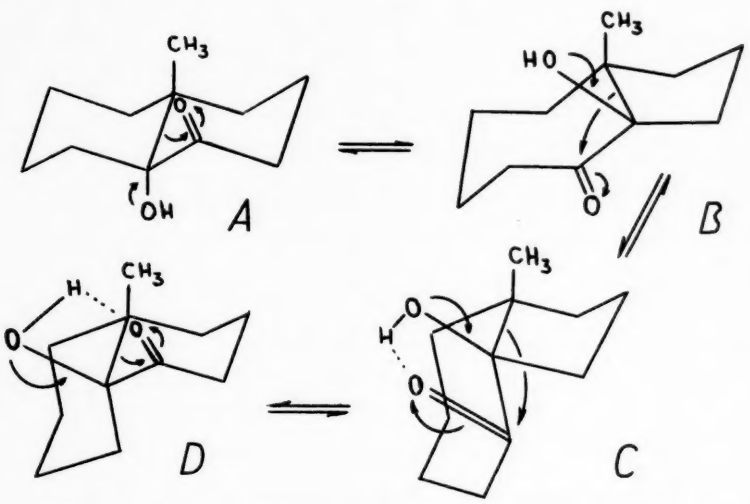
** These values were taken from: C. Djerassi, W. Closson and A.F. Lipman, J.Amer.Chem.Soc. 78, 3163 (1956); C. Djerassi and W. Closson, Ibid. 78, 3761 (1956).

Accepting that the perhydroazulene ketol is an intermediate in the reversible conversion of (VII, R=H) to (VI, R=H) and taking into account the steric requirements of a concerted electron shift we propose a reaction course described in the reaction scheme on page 821.

Of the two conformations B and C of the cycloheptanone ring, C is stabilized by hydrogen bonding. The fact that V rearranges to (VI, R=H) with 2% methanolic potassium hydroxide, whereas (VII, R=H) is unchanged under the same conditions can explain why V is not found in the equilibrium mixture of (VI,R=H) and (VII, R=H).

Treatment of (VII, R=OH) with base resulted in its conversion to the 5β-isomer (VI, R=OH)[8] [(acetate (VI, R=OAc; m.p. 141-142° $[\alpha]_D$ - 16°)].

[8] This compound is identical with the diol-one described by I.M. Heilbron, E.R.H. Jones and F.S. Spring, J.Chem.Soc.801 (1937) and assumed to be (VI, R=OH); L.F. Fieser and M. Fieser, Steroids pp.297-298. Reinhold, New York (1959).



It is evident from Table 2 that in the ketols VI where the hydroxyl is equatorial to ring B, the carbonyl n→π* band and the maximum of the first extremem in the rotatory dispersion curve are shifted to shorter wavelength. Bathochromic shifts are observed for the ketols VII, where the hydroxyl is axial.[3,4] It is to be noted that the assumed conformation of V differs from that of the ketone I (and also from that of its 6αH isomer[1]) and hence the different sign and magnitude of its Cotton effect.

This type of decalin-perhydroazulene-ketol rearrangement is not confined to the steroid system and has been postulated to explain a number of conversions in other natural products, e.g. marrubin[9] and grayanotoxin I[10].

The analogous ketol rearrangements in the decalin series are being investigated.

Acknowledgements - We wish to thank Prof. F. Sondheimer and Syntex S.A. for the optical rotatory dispersion measurements and Dr. S. Pinchas for the infra-red measurements. This work was supported in part by the Kayser-Roth Foundation, New York, N.Y. U.S.A.

[9] D.G. Hardy, W. Rigby and D.P. Moody, J.Chem.Soc. 2955 (1957); W. Cocker, J.T. Edward, T.F. Holley and D.M.S. Wheeler, Chem. & Ind. 1485 (1955).

[10] H. Kakisawa, M. Kurono, S. Takahashi and Y. Hirata, Tetrahedron Letters No. 2, 59 (1961).

Tetrahedron Letters No. 22, pp.822-826, 1961. Pergamon Press Ltd. Printed in Great Britain.

THE STEREOCHEMISTRY OF MAYUMBINE AND STRUCTURALLY RELATED OXINDOLE ALKALOIDS[1]

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Ames, Iowa

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A RECENT chemical and proton magnetic resonance spectral study of ajmalicinoid indole alkaloids revealed that ajmalicine, its 3-iso derivative, tetrahydroalstonine and akuammigine represent the four possible stereochemical forms (III-VI, respectively) of the gross alkaloid structure I possessing 15α-H and 19α-methyl functions.[3] We now wish to report an extension of the PMR investigation to the indole base mayumbine (I)[4] and the structurally related oxindole alkaloids (II) formosanine,[5] mitraphylline and isomitraphylline,[5] which reflects their relative stereochemistry.

Previous data[4] and the lack of identity of the PMR spectrum of mayumbine with that of any of the compounds III-VI shows it to be the C (19)

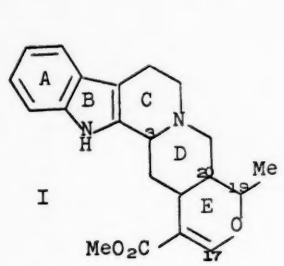
[1] This research was supported by a grant (M-1301) from the National Institutes of Health, Public Health Service, U.S. Department of Health, Education and Welfare.

[2] Present address: Department of Chemistry, Indiana University, Bloomington, Indiana.

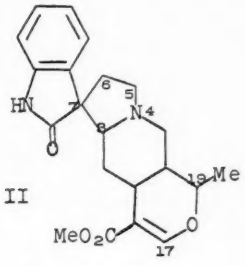
[3] E. Wenkert, B. Wickberg and C.L. Leicht, J.Amer.Chem.Soc. 83, in press (1961).

[4] M.M. Janot, R. Goutarel and J. Massonneau, C.R.Acad.Sci.,Paris 234, 850 (1952).

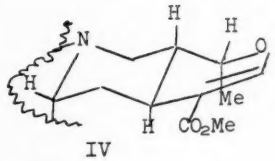
[5] J.C. Seaton, M.D. Nair, O.E. Edwards and L. Marion, Canad.J.Chem. 38, 1035 (1960) and references contained therein.



I



II



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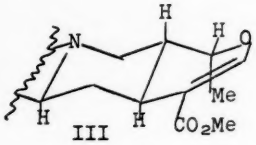
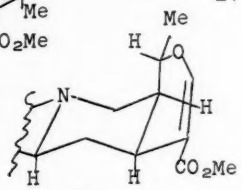
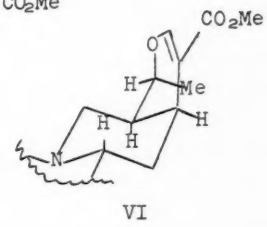


III



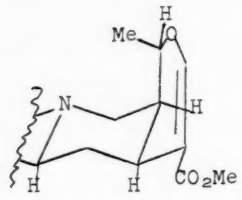
V



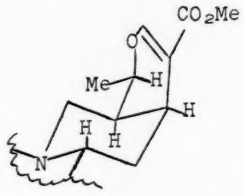
VI

epimer of one of the four bases. The absence of a one-proton downfield signal, characteristic of the equatorial C (3)-H of pseudo compounds,[3] eliminates 19-iso-IV, while the low spin-spin coupling constant ($J_{H\ (19)H\ (20)}$ = 2.6 cps) speaks against a 19,20-trans diaxial hydrogen arrangement and hence, eliminates both D/E trans structures, 19-iso-III and 19-iso-IV. Thus, mayumbine must be 19-isotetrahydroalstonine (VII) or 19-isoakuammigine (VIII). In contrast to the consistent chemical shift ($\delta = 4.41 \pm 0.08$) of the C (19)-H signal in all ajmalicinoid alkaloids inspected,[3] mayumbine and formosanine (II) have their one-proton octet centered farther upfield ($\delta = 3.76$). This $\Delta\delta$ indicates that the C (19) hydrogen is oriented more favourably for intramolecular shielding by the ring E double bond in these alkaloids than in any of their stereoisomers, a condition satisfied by the C (19)-H quasi-axial conformation in VIII. This argument and an independent one for formosanine (vide infra) support a 19-isoakuammigine (VIII)

structure for mayumbine.

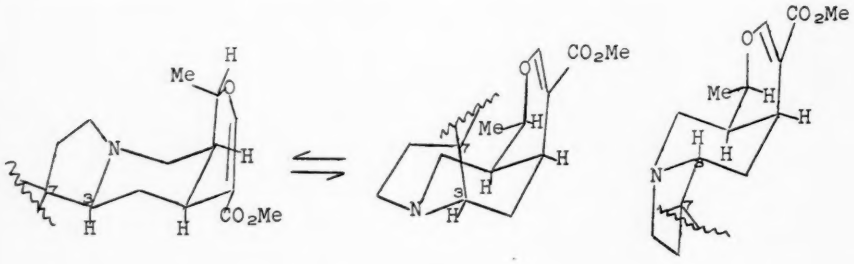


VII



VIII

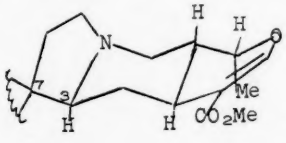
All PMR data relating to the C (19) evironment show formosanine (II) to be the oxindole analogue (IX or X) of amyumbine [Formosanine: C (19)-H octet at δ = 3.76 (J_{HH} = 2.9 cps) and C (19)-Me doublet at δ = 1.29 (J = 6.1 cps); mayumbine: C (19)-Me doublet at δ = 1.34 (J = 7.0 cps)]. Equilibration of formosanine and isoformosanine, a process affecting the asymmetric centers of only C (3) and/or C (7),[5,6] has revealed this pair of epimeric alkaloids to be of comparable stability [K(form./isoform.) = 4],[5] while a compound of the unstable configuration of IX, irrespective of its C (7) configuration, would be expected to be isomerized completely to X at equilibrium. As a consequence, formosanine possesses the 19-isoakuammigine stereochemistry depicted in X and isoformosanine its C (7) epimeric configuration.



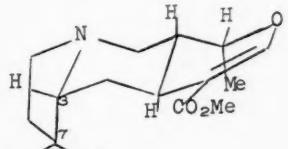
IX X

[6] E. Wenkert, J.H. Udelhofen and N.K. Bhattacharyya, J.Amer.Chem.Soc. 81, 3763 (1959).

The PMR spectra of mitraphylline (II) and isomitraphylline (II), another C (3) and/or C (7) isomeric pair of oxindole alkaloids,[5] show these substances to be related stereochemically to ajmalicine (III) or 3-iso-ajmalicine (IV) [C (19)-H octet: mitrophylline— $\delta = 4.34$ ($J_{HH} = 2.5$ cps), isomitraphylline— $\delta = 4.39$ ($J_{HH} = 2.4$ cps), III— $\delta = 4.44$ ($J_{HH} = 2.7$ cps),[3] IV— $\delta = 4.38$ ($J_{HH} = 1.8$ cps).[3] C (19)-Me doublet: mitraphylline— $\delta = 1.11$ ($J = 6.4$ cps), isomitraphylline— $\delta = 1.13$ ($J = 6.3$ cps), III— $\delta = 1.16$ ($J = 6.0$ cps),[3] IV— $\delta = 1.19$ ($J = 7.0$ cps)[3]]. A distinction between the resulting stereoformulas XI and XII can be made on the basis of available equilibrium data. As in the case of the formosanines (vide supra) the mitraphyllines are of not too dissimilar energy content [K(mit./isomit.) = 4],[5] whereas, a compound of the pseudo configuration XII with a resultant axial quaternary C (3) substituent would be expected to be fully converted to XI at equilibrium. Hence, the ajmalicine stereochemistry depicted in XI and its C (7) isomeric configuration represent mitraphylline and isomitraphylline, respectively.



XI

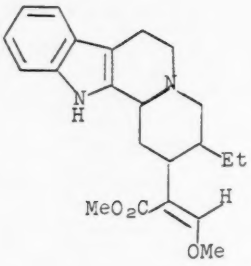


XII

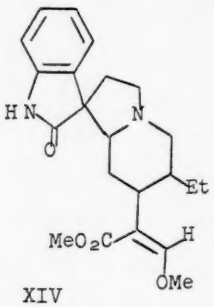
While the C (17) olefinic hydrogen appears in the PMR spectra of all ajmalicinoid indole alkaloids as a singlet at $\delta = 7.54 \pm 0.02$, it shows up at 7.32 p.p.m. in the spectra of the ring E seco alkaloids corynantheine and corynantheidine (XIII) and at 7.23 or 7.30 p.p.m. in the spectrum of rhyncophylline (XIV).[7] This upfield shift indicates that the methoxymethylene group in the seco alkaloids has the stereochemistry indicated in XIII and

[7] J.C. Seaton and L. Marion, Canad.J.Chem. 35, 1102 (1957) and references contained therein.

XIV.[8,9,10]



XIII



XIV

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[8] L.M. Jackman, Applications of Nuclear Magnetic Resonance Spectroscopy in Organic Chemistry pp.119-125. Pergamon Press, London (1959).

[9] The authors are most grateful to Dr. Raymond-Hamet for a gift of the oxindole alkaloids used in this investigation.

[10] The PMR spectra were obtained with ca. 25% deuterochloroform solutions on a Varian Model HR60 spectrometer at 60 mc/sec with tetramethylsilane acting as internal standard. The position of major peaks was determined by the audiofrequency sideband technique, that of minor peaks by linear interpolation.

Tetrahedron Letters No. 22, pp.827-829, 1961. Pergamon Press Ltd. Printed in Great Britain.

REDUCTION OF HEXACHLOROACETONE BY 1-BENZYL-1,4-DIHYDRONICOTINAMIDE[1]

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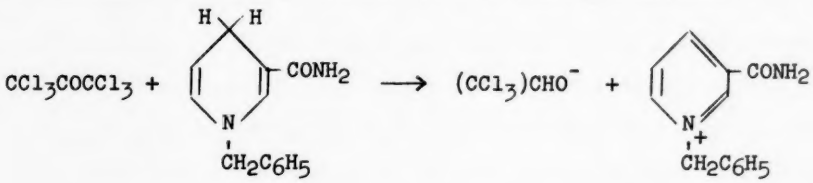
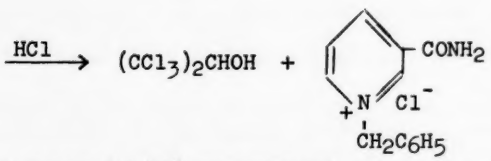
Philadelphia 4, Pennsylvania

(Received 23 November 1961)

HEXACHLOROACETONE is very readily reduced to hexachloroisopropanol by 1-benzyl-1,4-dihydronicotinamide. The reduction goes violently at room temperature in the absence of solvent, is exothermic, and is accompanied by formation of a black tar. Even at 0° the reaction went vigorously.





Best yields (53-60%) were obtained in formamide in which the initial

[1] This reaearch was supported in part by a grant from the National Science Foundation.

[2] Present address, Central Research Department, E.I. du Pont de Nemours and Company, Wilmington, Delaware.

[3] National Science Foundation Summer Research Participant, 1961.

solubility of hexachloroacetone was low. The best yield of hexachloroisopropanol in the absence of solvent was 24%. Hydrolysis of the reaction mixtures with dilute hydrochloric acid gave hexachloroisopropanol (m.p. 87-87.5°), which was identified by its melting point, elemental analysis, infra-red spectrum, and mixed melting point with an authentic sample.[4] A blank run in formamide in which the dihydro compound was absent gave no hexachloroisopropanol. Nicotinamide-1-benzylochloride was identified by its melting point (232-238°), mixed melting point with an authentic sample (no depression), and by the identity of its infra-red spectrum with that of an authentic sample.

The reduction of a "true" ketone in good yield by a dihydronicotinamide model for the coenzyme, dihydrodiphosphopyridine nucleotide (dihydronicotinamide-adenine-dinucleotide), has not yet been accomplished. Pyruvic acid has been reduced to lactic acid in 5-7% yield by 5-(2,4-dinitrophenylthio)-1-(2,6-dichlorobenzyl)-1,4-dihydronicotinamide.[5] Alloxan is reduced rapidly, although in unstated yield, by 1-methyl or 1-n-propyl-1,4-dihydronicotinamide in water at 0° and pH 6-11.[6] Pyruvic acid,[6,7] benzoylformic acid[7] and benzil[8] are reduced in low yield by 2,6-dimethyl-3,5-dicarboethoxy-1,4-dihydropyridine, which is not strictly analogous to a 1-substituted dihydronicotinamide. The olefinic double bond of 1-phenyl-4,4,4-trifluoro-2-buten-1-one is reduced in good yield by 1,2,6-trimethyl-

[4] M. Geiger, E. Usteri and C. Grünacher, Helv.Chim.Acta 34, 1335 (1951); W. Gerrard and B.K. Howe, J.Chem.Soc. 505 (1955); O. Neunhoeffer and A. Spange, Liebigs Ann. 632, 22 (1960).

[5] K. Wallenfels and D. Hofmann, Tetrahedron Letters No. 15, 10 (1959).

[6] D. Mauzerall and F.H. Westheimer, J.Amer.Chem.Soc. 77, 2261 (1955).

[7] R. Abeles and F.H. Westheimer, J.Amer.Chem.Soc. 80, 5459 (1958).

[8] E.A. Braude, J. Hannah and R. Linstead, J.Chem.Soc. 3257 (1960). The reduction of benzil in low yield by 1-benzyl-1,4-dihydronicotinamide in the absence of solvent has been observed by J.M. Kolyer, Ph.D. Thesis, University of Pennsylvania, p.159 (1960).

3,5-dicarboethoxy-1,4-dihydropyridine.[9]

The ready reduction of hexachloroacetone reported here may be attributed to an increase in the positive character of the carbonyl carbon. The facile reduction of thiobenzophenones by 1-benzyl-1,4-dihydronicotinamide is suggested as being caused by the greater polarity of the thiocarbonyl group.[10] Previous work on the reduction of aromatic nitro and nitroso compounds has indicated that the more electron-deficient the nitrogen atom was, the more readily the group was reduced by 1-substituted dihydronicotinamides.[11] The electron-withdrawing trifluoromethyl group promotes the nonenzymic reduction of a double bond by 1,2,6-trimethyl-3,5-dicarboethoxy-1,4-dihydropyridine.[9]

Chloral is reduced in 3% yield to 2,2,2-trichloroethanol by 1-benzyl-1,4-dihydronicotinamide in the absence of solvent or in chloroform or acetone. The alcohol was identified by gas chromatography and by comparison of its infra-red spectrum with that of an authentic sample.

When the reduction of hexachloracetone was done in acetone, nitromethane or cyclohexene, nicotinamide-1-benzylochloride precipitated quickly; in the case of cyclohexene a yield in excess of 90% was formed within 15 min but no hexachloroisopropanol was detected. The yield of chloride ion in cyclohexene solvent appears to be a function of the purity of the cyclohexene.

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[9] B.E. Norcross, P.E. Klinedinst, Jr. and F.H. Westheimer, Abstracts of Papers, p.74 Q. 140th Meeting, American Chemical Society, Chicago, Illinois, September, 1961.

[10] R.H. Abeles, R.F. Hutton and F.H. Westheimer, J.Amer.Chem.Soc. 79, 712 (1957).

[11] D.C. Dittmer and J.M. Kolyer, J.Org.Chem. In press.